ORIGINAL SUBMISSION

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BURDOCK GROUP
Toxicology and Risk Assessment

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January 12, 2004

04-02-03P03:20 RCVD

Robert Martin, Ph.D.
Deputy Division Director
Division of Biotechnology and GRAS Notification Review
Office of Food Additive Safety, HFS-200
Center for Food Safety and Applied Nutrition
US Food and Drug Administration
5100 Paint Branch Parkway
College Park, MD 20740-3835
T: 202-418-3074
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Dear Dr. Martin,

In accordance with proposed 21 CFR §170.36 (Notice of a claim for exemption based on a GRAS determination) published in the Federal Register (62 FR 18937-18964), I am submitting in triplicate, as the representative of the notifier, Linguagen Corp, 2005 Eastpark Boulevard, Cranbury, NJ 08512-3515, a GRAS notification of AMP (Adenosine 5'-monophosphoric acid and its monosodium and disodium salts) as a food and beverage flavor enhancer (flavor modifier), at specified levels that would result in a total added AMP consumption not to exceed 680 mg *per* day as AMP. A full copy of the GRAS panel report, as defined in 21CF§170.30, setting forth the basis for the GRAS determination, and CV's of the members of the GRAS panel for review by the Agency, are also enclosed.

Sincerely

James C. Griffiths, Ph.D., DABT, CBiol FIBiol
Director of Toxicology
Burdock Group

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## 1. GRAS Exemption Claim

### A. Claim of Exemption from the Requirement for Premarket Approval Pursuant to Proposed 21 CFR §170.36(c)(1).

AMP (Adenosine 5'-monophosphoric acid and its monosodium and disodium salts) has been determined to be generally recognized as safe (GRAS) and, therefore, exempt from the requirement of premarket approval, under the conditions of its intended use as described below. The basis for this finding is described in the following sections

1/28/04

James C. Griffiths, Ph.D., DABT, CBiol FIBiol — Date
Director of Toxicology
Burdock Group

### (i) Name and Address of the Notifier

James C. Griffiths, Ph.D., DABT, CBiol FIBiol
Director of Toxicology
Burdock Group
780 US Highway 1, Suite 300
Vero Beach, Florida 32962

Telephone: 772-62-3900, ext. 109
Facsimile: 772-562-3908
E-Mail: jgriffiths@burdockgroup.com

### (ii) Common Name of the Notified Substance

AMP; AMP (Adenosine 5'-monophosphoric acid and its monosodium and disodium salts).

### (iii) Conditions of Use

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AMP (Adenosine 5'-monophosphoric acid and its monosodium and disodium salts) used as a food and beverage flavor enhancer (flavor modifier), at specific use levels that would result in a total added AMP consumption not to exceed 680 mg *per* day as AMP. The specific food categories to which this material will be added, the 21 CFR regulatory citation and the use levels are: Chewing gum, including all forms (21CFR§170.3(n)(6))-173 ppm; Coffee and tea, including regular, decaffeinated, and instant types (21CFR§170.3(n)(7))-173 ppm; Snack foods, including chips, pretzels, and other novelty snacks (21CFR§170.3(n)(37))-800 ppm; Soups and soup

mixes, including commercially prepared meat, fish, poultry, vegetable, and combination soups and soup mixes (21CFR§170.3(n)(40))-173 ppm; Sugar substitutes, including granulated, liquid, and tablet sugar substitutes (21CFR§170.3(n)(42))-400 ppm; Salt substitute (potassium chloride) – 400 ppm.

AMP will qualify as an ingredient exempted from the requirement for declaration on the food label/labeling under 21CFR§101.4(b)(1) as it is a flavoring under the definitions of 21CFR§101.22.

The estimated mean and 90$^{th}$ percentile intake of AMP (Adenosine 5'-monophosphoric acid and its monosodium and disodium salts) by the total population from all proposed uses at the maximum use levels as a food and beverage flavor enhancer (flavor modifier) was determined to be 149 and 307 mg/person/day, respectively. Purines, the class of compounds that includes AMP, are currently consumed in the diet at mean and 90$^{th}$ percentile intake levels of 560 and 1120 mg purines/person/day, respectively. Combining the current and added intakes gives a total mean purine consumption. The estimated total mean and 90$^{th}$ percentile consumption of purine, if AMP is added to the selected foods at the levels specified in the preceding paragraph, would be 709 mg/day and 1427 mg/day, respectively.

**(iv) Basis of the GRAS Determination**

Pursuant to 21CFR §170.3, AMP (Adenosine 5'-monophosphoric acid and its monosodium and disodium salts) has been determined GRAS by scientific procedures for its intended conditions of use. The safety of AMP (Adenosine 5'-monophosphoric acid and its monosodium and disodium salts) is supported by the widespread intentional use of purines in the diet, *i.e.*, purines have been used as flavoring agents in Japan since antiquity. The primary constituent in the traditional Japanese seasoning, dried bonito, is inosine 5'-monophosphate (IMP). Commercial production of IMP and guanosine 5'monophosphate (GMP) as food flavoring agents began in Japan in 1960. They are produced either by hydrolysis of purified yeast RNA followed by purification or by chemical synthesis. The European Community has approved the nucleotide acids and sodium salts of AMP, GMP, IMP, CMP (cytidine 5'-monophosphate) and UMP (uridine 5'-monophosphate) as food additives that may be added for specific nutritional purposes in foods for particular nutritional uses. In the United States, AMP, CMP, UMP and disodium GMP are added to some infant formulas.

This determination is based on the views of experts who are qualified by scientific training and experience to evaluate the safety of substances used as ingredients in food. The experts (and attached curriculum vitae) for this GRAS determination were:

Joseph F. Borzelleca, Ph.D., F.A.T.S.
Walter H. Glinsman, M.D.
John A. Thomas, Ph.D., F.A.T.S.

### (v) Availability of Information

The data and information that serve as a basis for this GRAS determination are available for the Food and Drug Administration's (FDA) review and copying at a reasonable time at the office of:

James C. Griffiths, Ph.D., DABT, CBiol FIBiol
Director of Toxicology
Burdock Group
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E-Mail: jgriffiths@burdockgroup.com

And/or

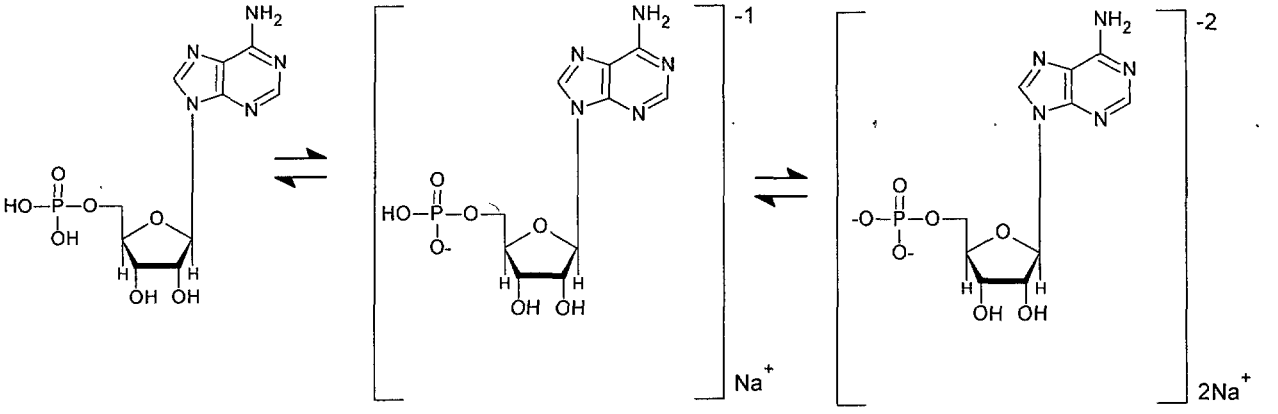
George A. Burdock, Ph.D., DABT, FACN
President
Burdock Group
888 Seventeenth Street, NW; Suite 810
Washington, DC 20006
Telephone: 202-785-8200
Facsimile: 202-785-8666
E-Mail: gburdock@burdockgroup.com

Alternatively, copies of data and information can be provided to FDA upon request, by contacting Dr. James Griffiths.

## 2. Detailed Information about the Identity of the Notified Substance

### A. Identity.

AMP is an endogenous purine nucleotide found in all living organisms. AMP is composed of the purine base adenine, covalently bound to a pentose sugar, forming adenosine, which is esterified with phosphoric acid in equilibrium to salt form with normal physiological and/or biochemical buffering ions, most notably sodium (Figure 1), such that the free acid nucleotide equilibrates in normal physiological and/or biochemical buffering systems to a salt form. One could either use the free acid form or the salt form as a food ingredient, knowing that the interconversion between the free acid and the salt occurs in the mixture and final food in relation to the buffering conditions of the milieu. The exposure and safety assessment in this document are applicable to AMP irrespective of the degree of dissociation of the equilibrium at the time of safety testing and/or food addition. For the remainder of this document, the term "AMP" will refer to all normal physiological and biochemical forms of AMP from this equilibrium.



**Adenosine 5'-monophosphoric acid** | **Adenosine 5'-monophosphate, monosodium salt** | **Adenosine 5'-monophosphate, disodium salt**

**Figure 1. Chemical structure of AMP (*i.e.*, adenosine 5'-monophosphate/adenosine 5'-monophosphoric acid/adenosine 5'-monophosphate, monosodium salt/adenosine 5'-monophosphate, disodium salt)**

Table 1 provides all CAS numbers identified as having been associated with AMP. As will be noted, AMP is used as a synonym for the acid form (phosphoric acid) as well as generic salt (phosphate) and specific salts (mono- and disodium salts).

**Table 1. CAS Numbers, Names and Synonyms for AMP**

| CAS Reg. No. | Name | Synonym | Synonym |
|---|---|---|---|
| 61-19-8 | Adenosine monophosphate | AMP[1] | Adenosine 5'-monophosphoric acid[2] |
| 18422-05-4 | Adenosine 5'-monophosphoric acid | AMP[3] | |
| 149022-20-8 | Adenosine 5'-monophosphate sodium salt | AMP[4] | Adenosine 5'-monophosphate, sodium salt from yeast[5]<br>Adenosine 5'-monophosphate, disodium salt[6] |
| 162756-82-3 | Alternate CAS | AMP[7] | |
| 47286-65-7 | Alternate CAS | AMP[8] | |
| 47287-97-8 | Alternate CAS | AMP[9] | |
| 53624-78-5 | Alternate CAS | AMP[10] | |
| 67583-85-1 | Alternate CAS | AMP[11] | |

[1] = http://chemfinder.cambridgesoft.com/result.asp; [2] = http://chem.sis.nlm.nih.gov/chemidplus
[3] = http://www.apolloscientific.co.uk/products/lifescience/otherProducts_Lifesciences_AMP.htm;
[4] = http://sigma-reporter.co.uk/pdfs/eChrome/T196905.pdf ; [5] = http://www.rose-hulman.edu/chemistry/000000/000473.pdf;
[6] = http://www.seqchem.com/catalogue.php; [7] = http://www.cdc.gov/niosh/rtecs/au7224b4.html;
[8] = http://www.cdc.gov/niosh/rtecs/au7224b4.html; [9] = http://www.cdc.gov/niosh/rtecs/au7224b4.html;
[10] = http://www.cdc.gov/niosh/rtecs/au7224b4.html; [11] = http://www.cdc.gov/niosh/rtecs/au7224b4.html;

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The general chemical descriptions for AMP, and its sodium salts are listed in Table 2.

**Table 2. General chemical description of AMP and its sodium salts.**

| | |
|---|---|
| Synonyms | Adenosine 5'-monophosphate/<br>Adenosine 5'-monophosphoric acid/<br>Adenosine 5'-monophosphate, monosodium salt/<br>Adenosine 5'-monophosphate, disodium salt<br>(See Table 1) |
| Functional use | Flavor enhancer (flavor modifier) |
| CAS Reg. No. | See Table 1 |
| Chemical formula | $C_{10}H_{14}N_5O_7P$; $C_{10}H_{13}N_5O_7PNa$; $C_{10}H_{12}N_5O_7PNa_2$ |
| Molecular weight | 347; 369; 391 |

CAS = Chemical Abstracts Service

## B. Composition.

AMP is primarily isolated from hydrolyzed yeast (*e.g., Saccharomyces cerevisiae* or *Candida utilis,* or similar food approved strain) ribonucleic acid (RNA). The AMP is isolated by ion-chromatographic separation using aqueous buffers and dried into a crystallized 99% pure AMP powder.

## C. Method of Manufacture.

AMP is manufactured according to current Good Manufacturing Practice (cGMP) with all the reagents used in the process conforming to FCC[1] specifications. Key elements of the primary manufacturing process are diagramed in Figure 2. AMP is isolated from hydrolyzed yeast (*e.g., Saccharomyces cerevisiae* or *Candida utilis,* or similar food approved strain) ribonucleic acid (RNA). The yeast is grown in fermentation culture, pelleted and autolysed by exposure to salt and heat. This process produces an RNA-rich yeast extract. The RNA is hydrolyzed with pancreatic ribonuclease (RNAse) enzyme, which liberates the AMP. The AMP is isolated by ion-chromatographic separation using aqueous buffers and dried into a crystallized 99% pure AMP powder.

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[1] Food Chemicals Codex

**Figure 2. Manufacturing process for AMP.**

## D. Specifications for Food Grade Material.

Batch analysis from four different lots indicates that the current manufacturing process consistently produces AMP that meets the specifications indicated in Table 3, which are equivalent to the FCC specifications for disodium inosinate, an analogous nucleotide (FCC, 1996).

**Table 3. Adenosine 5'-monophosphate specifications**

| Test | Specification | Result (N=4) |
|---|---|---|
| Appearance | White powder | Conforms |
| Identification/Assay | HPLC | Passed |
| Purity | Minimum 95% based on HPLC and enzymatic assays | 99% |
| Clarity and Color of Solution | Passes test | Passed |
| Other nucleotides and amino acids | Maximum 5% | Passed |
| Ammonia salts | Passes test | Passed |
| pH | 5.0-6.0 | Passed |
| Barium | Not more than 0.015% | <0.0001% |
| Lead | Not more than 10 mg/kg. | <0.50 ppm |
| Heavy Metals (as Pb) | Not more than 0.002%. | <0.50 ppm |

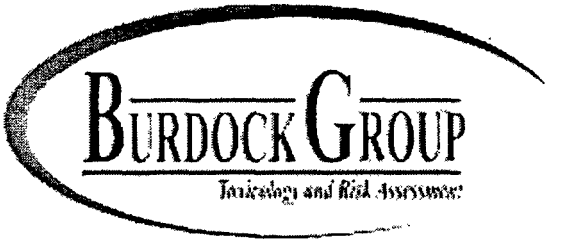
ppm=parts *per* million

## 3. Self Limiting Levels of Use.

As AMP levels increase it contributes a strong 'savory, umami-like flavor' that can result in undesired off-flavor notes in many applications. The end result is that if AMP is added to a food above its technologically self-limiting level, the food becomes unpalatable.

## 4. Basis of the GRAS Determination.

The determination that AMP (Adenosine 5'-monophosphoric acid and its monosodium and disodium salts) is GRAS is on the basis of scientific procedures. A full copy of the dossier - "Generally Recognized As Safe (GRAS) Status of AMP (Adenosine 5'-Monophosphoric acid and its monosodium and disodium salts) as a Food Flavor Enhancer (Flavor Modifier)" – as reviewed by the expert panel members, is attached.

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# GENERALLY RECOGNIZED AS SAFE (GRAS) STATUS OF AMP (ADENOSINE 5'-MONOPHOSPHORIC ACID AND ITS MONOSODIUM AND DISODIUM SALTS) AS A FOOD FLAVOR ENHANCER (FLAVOR MODIFIER)

**August 29, 2003**

**Panel Members**

**Joseph F. Borzelleca, Ph.D., F.A.T.S.**

**Walter H. Glinsmann, M.D.**

**John A. Thomas, Ph.D., F.A.T.S.**

Voice: 772-562-3900 Facsimile: 772-562-3908

www.burdockgroup.com

# GENERALLY RECOGNIZED AS SAFE (GRAS) STATUS OF AMP (ADENOSINE 5'-MONOPHOSPHORIC ACID AND ITS MONOSODIUM AND DISODIUM SALTS) AS A FOOD FLAVOR ENHANCER (FLAVOR MODIFIER)

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# GENERALLY RECOGNIZED AS SAFE (GRAS) STATUS OF AMP (ADENOSINE 5'-MONOPHOSPHORIC ACID AND ITS MONOSODIUM AND DISODIUM SALTS) AS A FOOD FLAVOR ENHANCER (FLAVOR MODIFIER)

## 1. SUMMARY

The undersigned, independent panel of recognized experts (hereinafter referred to as the Expert Panel)[1], qualified by their scientific training and relevant national and international experience to evaluate the safety of food ingredients, was requested by Linguagen Corp. to determine the Generally Recognized As Safe (GRAS) status of AMP (Adenosine 5'-monophosphoric acid and its monosodium and disodium salts) used as a food and beverage flavor enhancer (flavor modifier), at specified levels that would result in a total added AMP consumption not to exceed 680 mg *per* day as AMP. A comprehensive search of the literature for safety and toxicity information on AMP, and its sodium salts and, related purines was conducted by Burdock Group in September 2002 and is summarized in this report. This search and supporting documentation were made available to the Expert Panel. In addition, the Expert Panel independently evaluated materials submitted by Linguagen Corp. and other materials deemed appropriate and necessary. Following an independent, critical evaluation, the Expert Panel conferred and unanimously agreed to the decision described herein.

## 2. INTRODUCTION

AMP is an endogenous purine nucleotide found in all living organisms. AMP is composed of the purine base adenine, covalently bound to a pentose sugar, forming adenosine, which is esterified with phosphoric acid in equilibrium to salt form with normal physiological and/or biochemical buffering ions, most notably sodium (Figure 1).

Table 1 provides all CAS numbers identified as having been associated with AMP. As will be noted AMP is used as a synonym for the acid form (phosphoric acid) as well as generic salt (phosphate) and specific salts (mono- and disodium salts).

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[1] Modeled after that described in Section 201(s) of the Federal Food, Drug, and Cosmetic Act, as amended. See also attachments (*curriculum vitae*) documenting the expertise of the Panel members.

**Table 1. CAS Numbers, Names and Synonyms for AMP**

| CAS Reg. No. | Name | Synonym | Synonym |
|---|---|---|---|
| 61-19-8 | Adenosine monophosphate | AMP[1] | Adenosine 5'-monophosphoric acid[2] |
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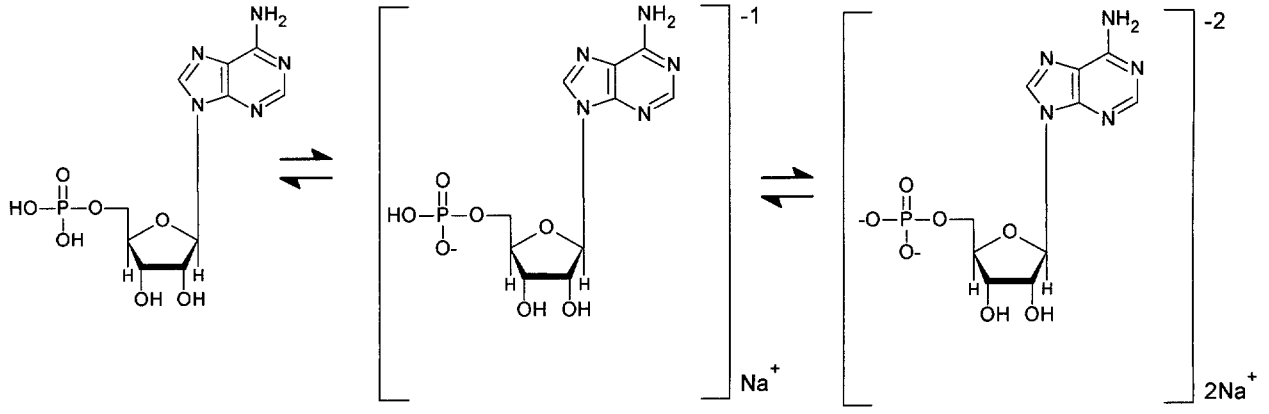
[1] = http://chemfinder.cambridgesoft.com/result.asp; [2] = http://chem.sis.nlm.nih.gov/chemidplus
[3] = http://www.apolloscientific.co.uk/products/lifescience/otherProducts_Lifesciences_AMP.htm;
[4] = http://sigma-reporter.co.uk/pdfs/eChrome/T196905.pdf ; [5] = http://www.rose-hulman.edu/chemistry/000000/000473.pdf;
[6] = http://www.seqchem.com/catalogue.php; [7] = http://www.cdc.gov/niosh/rtecs/au7224b4.html;
[8] = http://www.cdc.gov/niosh/rtecs/au7224b4.html; [9] = http://www.cdc.gov/niosh/rtecs/au7224b4.html;
[10] = http://www.cdc.gov/niosh/rtecs/au7224b4.html; [11] = http://www.cdc.gov/niosh/rtecs/au7224b4.html;

This unconventional nomenclature may, in part, also stem from the ease in which a free nucleotide acid equilibrates in normal physiological and/or biochemical buffering systems to a salt form. One could either use the free acid form or the salt form as a food additive, knowing that the interconversion between the free acid and the salt occurs in the mixture and final food in relation to the buffering conditions of the milieu. The exposure and safety assessment in this document are applicable to AMP irrespective of the 'side' of the equilibrium at the time of safety testing and/or food addition. For the remainder of this document, the term "AMP" will refer to all normal physiological and biochemical forms of AMP from this equilibrium.




**Adenosine 5'-monophosphoric acid** **Adenosine 5'-monophosphate, monosodium salt** **Adenosine 5'-monophosphate, disodium salt**

**Figure 1. Chemical structure of AMP (*i.e.*, adenosine 5'-monophosphate/adenosine 5'-monophosphoric acid/adenosine 5'-monophosphate, monosodium salt/adenosine 5'-monophosphate, disodium salt)**

Purines have been used as flavoring agents in Japan since ancient times. The primary constituent in the traditional Japanese seasoning, dried bonito, is inosine 5'-monophosphate (IMP) (Kojima, 1974). Commercial production of IMP and guanosine 5'monophosphate (GMP)

as food flavoring agents began in Japan in 1960. They are produced either by hydrolysis of purified yeast RNA followed by purification or, by chemical synthesis (Kojima, 1974).

The European Community has approved the nucleotide acids and sodium salts of AMP, GMP, IMP, CMP (cytidine 5'-monophosphate) and UMP (uridine 5'-monophosphate) as food additives that may be added for specific nutritional purposes in foods for particular nutritional uses (EC, 2001). In the Unites States, AMP, CMP, UMP and disodium GMP are added to some infant formulas (Abbott Laboratories, 2002).

The general chemical descriptions for AMP, and its sodium salts are listed in Table 2.

**Table 2. General chemical description of AMP and its sodium salts.**

| | |
|---|---|
| Systemic name | Adenosine 5'-monophosphate/<br>Adenosine 5'-monophosphoric acid/<br>Adenosine 5'-monophosphate, monosodium salt/<br>Adenosine 5'-monophosphate, disodium salt<br>(See Table 1) |
| Synonyms | See Table 1 |
| Functional use | Flavor enhancer (flavor modifier) |
| CAS Reg. No. | See Table 1 |
| Chemical formula | $C_{10}H_{14}N_5O_7P$; $C_{10}H_{13}N_5O_7PNa$; $C_{10}H_{12}N_5O_7PNa_2$ |
| Molecular weight | 347; 369; 391 |

CAS = Chemical Abstracts Service

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## 3. MANUFACTURING PROCESS AND SPECIFICATIONS

**Figure 1. Manufacturing process for adenosine 5'-monophosphate (AMP)**

Linguagen Corp. does not currently manufacture AMP. Rather, purified AMP is available as an item of commerce that may be obtained from specialty ingredient suppliers. Linguagen Corp.'s current supplier is Sigma-Aldrich, St. Louis, MO. It is currently prepared from yeast using a method similar to the one Linguagen Corp. proposes to use for future commercial production. Linguagen Corp. will manufacture AMP using current Good Manufacturing Practice with all the reagents used in the process conforming to FCC[2] specifications. Key elements of the manufacturing process are diagramed in Figure 1. AMP is isolated from hydrolyzed yeast (*e.g.*, *Saccharomyces cerevisiae* or *Candida utilis,* or similar food approved strain) ribonucleic acid (RNA). The yeast is grown in fermentation culture, pelleted and autolysed by exposure to salt and heat. This process produces an RNA-rich yeast extract. The RNA is hydrolyzed with pancreatic ribonuclease (RNAse) enzyme, which liberates the AMP. The AMP is isolated by ion-chromatographic separation using aqueous buffers and dried into a crystallized 99% pure AMP powder. Batch analysis from four different lots (See Appendix

[2] Food Chemicals Codex

1; (ABC, 2003))[3] indicates that the current manufacturing process consistently produces AMP that meets the specifications indicated in Table 3, which are equivalent to the FCC specifications for disodium inosinate, an analogous nucleotide (FCC, 1996).

**Table 3. Adenosine 5'-monophosphate specifications (See Appendix 1; ABC, 2003; Sigma-Aldrich, 2003)***

| Test | Specification | Result (N=4) |
|---|---|---|
| Appearance | White powder | Conforms |
| Identification/Assay | HPLC | Passed |
| Purity | Minimum 95% based on HPLC and enzymatic assays | 99% |
| Clarity and Color of Solution | Passes test | Passed |
| Other nucleotides and amino acids | Maximum 5% | Passed |
| Ammonia salts | Passes test | Passed |
| pH | 5.0-6.0 | Passed |
| Barium | Not more than 0.015% | <0.0001% |
| Lead | Not more than 10 mg/kg. | <0.50 ppm |
| Heavy Metals (as Pb) | Not more than 0.002%. | <0.50 ppm |

* Test methods available on request from Linguagen Corp.; ppm=parts *per* million

## 4. ESTIMATED DAILY INTAKE

The intake profile (amount and frequency) by individuals in USDA's Continuing Survey of Food Intakes by Individuals 1994-96, 98 (CSFII; USDA, 1998) was used to calculate the estimated daily intake (EDI) of AMP for individuals consuming the food groups selected for the addition of this AMP for this GRAS evaluation. These food groups as defined by the FDA (21 CFR 170.3(n)) are listed in Table 4.

**Table 4. Maximum intended use levels of AMP**

| Food Category* | Intended use level (ppm) |
|---|---|
| Chewing gum, including all forms** (6) | 173 |
| Coffee and tea, including regular, decaffeinated, and instant types (7) | 173 |
| Snack foods, including chips, pretzels, and other novelty snacks (37) | 800 |
| Soups and soup mixes, including commercially prepared meat, fish, poultry, vegetable, and combination soups and soup mixes (40) | 173 |
| Sugar substitutes, including granulated, liquid, and tablet sugar substitutes (42) | 400 |
| Salt substitute (potassium chloride) | 400 |

*The food categories correspond to those listed in 21 CFR 170.3(n). **The number in parenthesis following each food category is the paragraph listing in 21 CFR 170.3(n) for that food category.

[3] At the time this document was written, only four lots had been manufactured by the supplier (Sigma-Aldrich).

The means and 90th percentile EDIs were calculated for: (1) current purine intake from natural sources (current); (2) purine intake following addition of AMP to the selected food groups (added) and; (3) total estimated EDI from natural sources combined with levels from addition to the foods (total).

The mean purine consumption in the U.S., 560 mg/day, was calculated by Kojima (1974). The 90th percentile EDI of purine can be estimated by assuming two times greater consumption than the reported mean EDI (DiNovi and Kuznesof, 1995). Thus, the estimated 90th percentile EDI is 1120 mg purine *per* day.

If AMP is added to the selected foods at the levels specified in Table 4, the added mean and 90th percentile purine consumption will be 149 mg/day and 307 mg/day, respectively.

Combining the current and added intake levels gives the total mean purine consumption. The estimated total mean and 90th percentile consumption of purine, if AMP is added to the selected foods at the levels specified in Table 4, would be 709 mg/day and 1427 mg/day, respectively.

A statistical analysis of consumption of AMP from addition to potassium chloride (KCl) salt substitutes was not possible because consumption data are unavailable. Instead, consumption of AMP following addition to KCl salt substitutes was estimated from *per capita* consumption based upon average sales of salt substitutes from 2000 to 2002 (5,386,377 kg)[4] (Linguagen, 2003). Many of the KCl salt substitute products sold are actually seasoning mixes containing only a fraction of KCl. Nevertheless, the *per capita* consumption estimate was determined with the assumption that all of the salt substitute sold was 100% KCl. Therefore, the estimated *per capita* consumption will most likely overestimate KCl consumption rather than underestimate KCl consumption. Using this conservative approach, the daily *per capita* consumption of AMP from addition to KCl salt substitutes at the level specified in Table 4 would be 0.009 mg/day[5]. Thus, the contribution of AMP from addition to salt substitutes to the total daily AMP consumption is negligible.

**Table 5. Current purine intake, predicted purine intake following AMP addition to selected foods at the indicated levels (Table 4) and total purine intake (predicted + current) for individuals consuming foods selected for AMP addition**

| | *Per* User (mg/day) | |
|---|---|---|
| **Purine intake from:** | **Mean** | **90th Percentile** |
| Current | 560 | 1120 |
| Possible maximum consumption following addition of AMP (Table 4) | 149 | 307 |
| Total | 709 | 1427 |

[4] This is an overestimation of KCl intake because it is based on the assumption that 100% of all salt substitutes consist of KCl, but in fact the leading brand is a seasoning blend that does not contain KCl.

[5] Based on the 2000 US population of 281,421,906

Also considered was the addition of AMP in excipient formulations (21 CFR 170.3(o)(14)) in approved prescription drugs and approved over-the-counter (OTC) drugs. The Expert Panel believes consumption of AMP from its use in excipient formulations in prescription drugs and OTC drugs will be at levels that will not contribute to an overall AMP consumption that will exceed the acceptable daily intake as described in Section 6 (Risk Evaluation).

## 5. BIOLOGICAL DATA

The first step in AMP metabolism in the gastrointestinal (GI) tract is deamination of AMP to form 5'-inosine monophosphate (IMP) (Figure 3). Therefore, the studies summarized below are those on AMP, as well as its initial metabolite, IMP. In some of the studies, the amount of AMP or IMP in the diets was reported as a percentage of the diet, and in such cases, the levels were converted into mg/kg/day using comparative mammalian reference values for relative dose calculations established by the US Environmental Protection Agency (Derelanko and Hollinger, 2001; EPA, 1985). The average weight of humans was considered to be 60 kg.

### 5.1. Absorption, distribution, metabolism and elimination (ADME)

The normal human diet is abundant in DNA and RNA. Ribonucleic acids are degraded into nucleotides, nucleosides and free bases by the GI microflora and mucosa prior to absorption. A significant portion of AMP is degraded by intestinal flora or metabolized by GI mucosa before absorption. Up to fifty *percent* of radiolabeled dietary purine was degraded and lost as $CO_2$ within 30 minutes, with the remaining radiolabel being recovered in the urine (43%) and the feces (5%) (Simmonds, 1999). A majority of absorbed adenosine, its nucleotides and nucleosides, are rapidly degraded and converted to uric acid by the intestinal mucosal's battery of enzymes during passage and, released as such, in serosal secretions (Figure 3) (Brody, 1999; Simmonds, 1999). In non-primate mammals, hepatic uricase degrades uric acid into the extremely soluble allantoin (Simmonds, 1999). Because primates do not express uricase, uric acid is the end product of purine metabolism.

Wilson and Wilson (1965) observed complete degradation of AMP into uric acid and on to allantoin using isolated small segments of rat intestine from dams and their pups. This study demonstrated that all of the AMP degradation enzymes (nucleotide phosphorylase, adenosine deaminase, xanthine oxidase and presumably, uricase) were expressed in neonatal and adult rats. In an earlier report, these same authors noted that no detectable absorption of purines, including AMP, took place in the mucosa of segmented everted intestinal sacs of adult rats or hamsters (Wilson and Wilson, 1962). These studies indicate that purines are metabolized prior to or during intestinal absorption.

Following absorption, any intact purines and their metabolites are further rapidly metabolized and excreted. In pigs, up to 50% of radiolabelled dietary purine was degraded and expired as $CO_2$ within 30 min, the remaining 43% being recovered in the urine, with 5% in the feces (Simmonds, 1999). The half-life of [$8^{14}$C] IMP was approximately 5 hours in male and pregnant (day 10 or 18 of gestation) rats given 25 mg/kg by gavage (Ohara *et al.*, 1973). IMP peak levels were measured at 2.5 hours with nearly complete elimination by 24 hours. About 70% of total radioactivity appeared in the urine, 6-7% in feces, none in expired air, between 0-2% remained in organs, 8-17% in the organ-free carcass and 0.77% in the fetuses.

When male rats (N=5/group; N=10/control; strain not identified) were fed 0, 500 or 2000 mg/kg/day IMP for five or ten days (Hashimoto and Ishii, 1973), there were no differences in urine or serum uric acid levels in the treated rats compared with controls. Most of the exogenously ingested IMP was rapidly excreted in the urine as allantoin. Liver hypoxanthine-guanine phosphoribosyl transferase and adenine phosphoribosyl transferase activity were increased along with the ratio of liver uricase/xanthine oxidase activity, suggesting IMP metabolism by shunt pathways.

Endogenously synthesized AMP is degraded to adenosine and hypoxanthine with the majority being reused for the synthesis of ATP in the purine salvage pathway. This is catalyzed by adenine phosphoribosyl transferase (PRPP) which converts adenine to AMP and pyrophosphate (Brody, 1999). AMP released from cells undergoes hydrolysis by ectoenzyme 5'-nucleotidase, a ubiquitous cell plasma membrane enzyme, producing adenosine (Gordon *et al.*, 1989). Any adenosine not taken back up into the cell or not used in the salvage pathway is degraded to its end product, uric acid, and excreted in the urine. AMP is also rapidly dephosphorylated to adenosine through the action of nonspecific phosphatases, such as alkaline phosphatase (Fox and Kelley, 1978).

Data on the serum uric acid levels in humans indicate that the mean values for normal men (N=969) and women (N=168) were 5.0 mg/dL and 4.04 mg/dL, respectively (Grayzel *et al.*, 1961). Several investigators have suggested an upper limit for serum uric acid that ranges from 6.8 mg/dL to 7.5 mg/dL for men and 5.7 mg/dL to 6.35 mg/dL for women (Gjörup *et al.*, 1955; Grayzel *et al.*, 1961; Zöllner, 1963). This is in agreement with uric acid's upper limit of solubility in blood of approximately 7 mg/dL (Maesaka and Fishbane, 1998). In adults, approximately 30% of the uric acid produced daily is excreted in the bile and degraded in the GI tract by bacteria through a process called uricolysis; the remaining 70% is excreted through the kidneys (Sörensen, 1960). Excretion of urinary uric acid over 24 hours was 8.1 mg/kg for men and 8.0 mg/kg for women (Cockburn, 1961).

Inhibitors of adenosine metabolism include methylxanthines, such as caffeine and the anti-asthmatic drug, theophylline, that have been reported to antagonize the metabolism of adenosine (Osswald *et al.*, 1995) and the ADP receptor antagonist, dipyridamole, reportedly slows the metabolism of adenosine by preventing cellular uptake (Crutchley *et al.*, 1980).

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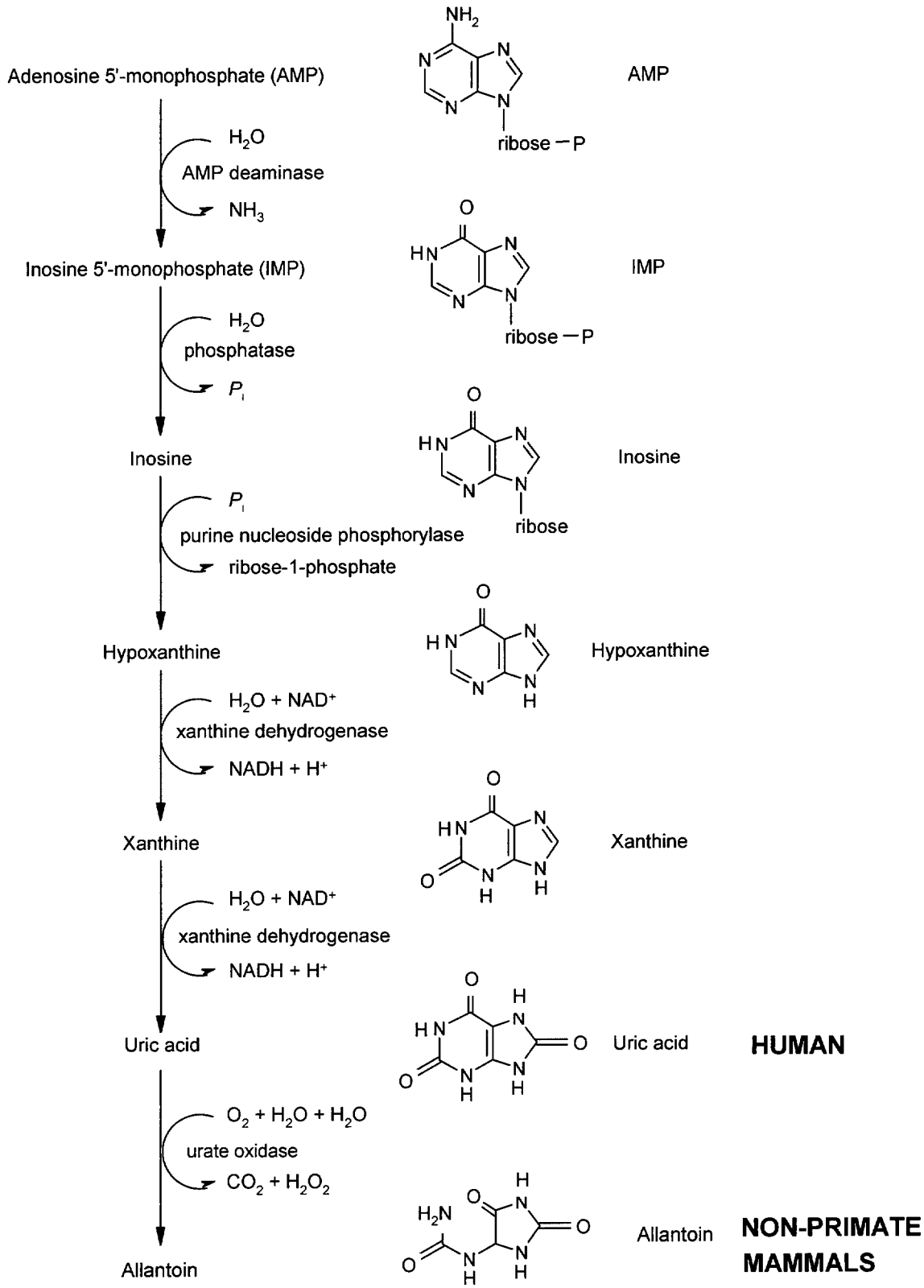


**Figure 3. Metabolism of adenosine 5'-monophosphate (AMP) (Brody, 1999)**

### 5.2. Biochemical/ Pharmacological effects

Purines are well-established cell signaling molecules that act through three families of purinergic receptors. These receptors are divided into the P1 receptors, mainly binding adenosine, and the ligand-gated ion-channel P2X receptors and P2Y G-protein-coupled receptors that have a greater affinity for ATP, ADP and UTP (reviewed in Burnstock, 2002). In the cardiovasculature, adenosine activation of P1 receptors affects local control of vessel tone and causes vasodilation. Intravenous infusion of 6 to 12 mg adenosine is currently used to reverse supraventricular tachycardia (PDR, 2002). In the kidney, binding of adenosine to P2 purinoceptors following *i.v.* infusion can cause vasoconstriction (Osswald *et al.*, 1995). Adenosine diphosphate (ADP) binding to P2 receptors induces platelet aggregation (Gachet, 2001).

Inhalation of adenosine reportedly elicits a concentration-dependent airflow limitation in asthmatics possibly through activation of P1 receptors on intermediary inflammatory cells such as mast cells and afferent nerve endings (Van Schoor *et al.*, 2000). Antagonism of P1 receptors is currently being pursued for novel anti-asthma medications and is the underlying mechanism for the activation of theophylline (Burnstock, 2002). Consumption of AMP has not induced bronchiolar constriction in asthmatics, thus AMP's asthma-inducing effects following inhalation are not relevant to assessing the safety of AMP as a food ingredient.

5'-Inosine monophosphate (IMP)-induced hypotension in the rabbit and dog following intravenous administration (Flossner, 1934), but had no effect on heart rate and ECG of the rabbit (Hara *et al.*, 1966; Yabo, 1964). Versprille (1966) reported no effect from IMP on the S-A or A-V nodes in the Langendorff preparation in the isolated rat heart. Isolated guinea pig intestine motility was decreased upon exposure to a 1% IMP solution (10,000 ppm) (Hara *et al.*, 1966). Isolated guinea pig uterus showed a biphasic response to the application of IMP (Flossner, 1934). In rats and cats, topical IMP enhanced the electrical response of the chordotympani to topical monosodium glutamate (MSG) (Adachi, 1964; Sato M *et al.*, 1965). Intravenous IMP had no significant effect on blood electrolytes in the rabbit (Hara *et al.*, 1966).

Kojima (1974) reported the following observations from studies on disodium 5'-inosinate (IDP). In mice, 500 mg/kg bolus *i.v.* dose caused (1) behavioral excitement, (2) increased reflex response, (3) lack of muscular relaxation, (4) depressed rotating activity during the first hour, (5) inability to modify electroshock convulsions and (6) dose-dependently decreased the metrazol convulsive dosage. Doses of 50-500 mg/kg *i.v.* prolonged loss of righting reflex. One hundred (100) mg/kg *s.c.* depressed salivary secretion, but had no effect on intestinal transport as measured by charcoal transportation. In rats, 100 mg/kg *s.c.* had no effect on gastric juice volume, but slightly increased pH. Rats given 100 mg/kg intragastric IDP showed no diuresis. Oral 500 mg/kg IDP had no effect on analgesic response of mice or carrageenan edema in rats. In cats, 10 and 50 mg/kg *i.v.* had no effect on blood pressure, heart rate, ECG or blood flow of hind limbs. IDP ($10^{-4}$ g/ml) did not affect the contractile response of guinea-pig ileum to acetylcholine, histamine or barium chloride, but $10^{-2}$ IDP decreased motility.

## 5.3. Safety studies

### 5.3.1. Acute studies

Acute lethal toxicity studies on inosine monophosphate indicated that it was practically non-toxic by the oral route with $LD_{50}$s ≥ 12 g/kg in rats and mice (Table 6). Regardless of the route, species or sex, near-lethal doses produced depression, clonic convulsion and dyspnea. Near-lethal doses by oral administration or intraperitoneal injection induced diarrhea and writhing. Surviving animals recovered from the clinical signs by 16 hours (Kojima, 1974).

**Table 6. Acute lethal toxicity studies on inosine monophosphate (IMP)**

| Animal | Route* | $LD_{50}$ (mg/kg) | Reference |
|---|---|---|---|
| Mouse | *p.o.* | 12 000-14 000 | Hara *et al.* (1966) |
| | *p.o.* (male) | 17 600 | Ichimura & Muroi (1973) |
| | *p.o.* (female) | 19 800 | Ichimura & Muroi (1973) |
| | *s.c.* | 6 200-7 000 | Hara *et al.* (1966) |
| | *s.c.* (male) | 5 480 | Ichimura & Muroi (1973) |
| | *s.c.* (female) | 5 630 | Ichimura & Muroi (1973) |
| | *i.p.* | 5 400-5 600 | Hara *et al.* (1966) |
| | *i.p.* (male) | 6 300 | Ichimura & Muroi (1973) |
| | *i.p.* (female) | 6 200 | Ichimura & Muroi (1973) |
| | *i.v.* | 3 300-3 900 | Hara *et al.* (1966) |
| | *i.v.* (male) | 3 950 | Ichimura & Muroi (1973) |
| | *i.v.* (female) | 4 600 | Ichimura & Muroi (1973) |
| Rat | *p.o.* | 16 000 | Usui *et al.* (1971) |
| | *p.o.* (male) | 17 100 | Ichimura & Muroi (1973) |
| | *p.o.* (female) | 15 900 | Ichimura & Muroi (1973) |
| | *s.c.* (male) | 3 900 | Ichimura & Muroi (1973) |
| | *s.c.* (female) | 4 340 | Ichimura & Muroi (1973) |
| | *i.p.* (male) | 5 400 | Ichimura & Muroi (1973) |
| | *i.p.* (female) | 4 850 | Ichimura & Muroi (1973) |
| | *i.v.* (male) | 2 730 | Ichimura & Muroi (1973) |
| | *i.v.* (female) | 2 870 | Ichimura & Muroi (1973) |

* *s.c.*, subcutaneously; *i.p.*, intraperitoneally; *i.v.*, intravenously; *p.o.*, perorally

Pregnant ICR-JCL mice (N=20) and SD-JCL rats (N=20-25) were treated with 0, 5, 50, 100, 300 or 500 mg/kg (mice) or 0, 5, 50, 100, 200 or 400 mg/kg (rats) AMP from gestation day 7 to gestation day 13 by intraperitoneal injections (Hashimoto *et al.*, 1970). In mice, no adverse effects were observed, at any dose, on erythrocytes, leucocytes or hematocrits. Hemoglobin was slightly elevated only at 500 mg/kg AMP with no effects at lower doses. In rats, no adverse effects were observed, at any dose, on erythrocytes, hemoglobins or hematocrits. Leukocyte numbers were elevated at 400 mg/kg AMP with no effects at lower doses.

### 5.3.2. Subchronic studies

Male rats (N=10/group; strain not specified) were fed 0, 10, 100 or 1000 mg/kg/day naturally or synthetically-derived IMP for 90 days (Hara *et al.*, 1966). There were no adverse effects on weight gain, weight or volume of cerebrum, cerebellum, thyroid, heart, stomach, liver, spleen, kidney, adrenal, testis, epididymis or urinary bladder, weight of lung or 'length of tail' in comparison with control group. No histological changes in internal organs were found by

macroscopic and microscopic examination. The No Observed Adverse Effect Level (NOAEL) in this rat study was 1000 mg/kg/day, the highest dose tested.

Male rats (N=10/group; strain not specified) were fed 0, 50 or 500 mg/kg/day IMP for 12 weeks or 24 weeks (Usui *et al.*, 1971). There were no adverse effects in treated rats compared with control on food intake, weight gain, organ weights, hematological parameters (erythrocyte/leukocyte counts, hemoglobin, hematocrit), clinical chemistry (total protein, urea nitrogen), urine parameters (pH, protein, glucose) or macroscopic and microscopic examination of visceral organs. The NOAEL in this rat study was 500 mg/kg/day, the highest dose tested.

Yonetani *et al.* (1973) reported the results from a 25 week feeding study in which Sprague-Dawley rats (N=8/group/sex) were fed 0, 250, 500, 1000 or 2000 mg/kg/day IMP for the first 12 weeks followed by 0, 400, 750, 1500 or 3000 mg/kg/day IMP for the remaining 13 weeks. There were no effects on behavior, body weight gain, food intake, hematology and urinalysis. One rat in the highest dose group died of a spontaneous nephroblastoma. Some animals in higher dosage groups showed renal medullary calcification. However, glomerulonephritis was observed in some animals from all of the groups with no significant differences noted. Organ weights were normal, but the relative mean weight of kidney and spleen in the 3000 mg/kg/day group were significantly higher than the other dose groups. The NOAEL from this rat study was 1500 mg/kg/day.

There were no adverse effects reported in male and female Beagle dogs fed IMP at ~1000 mg/kg/day (3.6-3.9% of diet) or ~2000 mg/kg/day (8% of diet) for four to six weeks (no other details provided) (Rivett *et al.*, 1973).

**5.3.3. Chronic studies**

The effects of dietary IMP were studied in Sprague-Dawley rats (N=6/sex/group) fed 0, 500, 1000, 2000 or 4000 mg/kg/day for 52 weeks (Yonetani *et al.*, 1973). There was a slight (non-statistically significant) decrease in body weight gain in the 4000 mg/kg dose group starting at week 42, but not at the lower dose groups. No clinical signs of adverse effects were observed and food consumption was the same in all groups throughout the study. At study termination, no significant abnormalities were observed in hematology (hematocrit, hemoglobin, red cell count, white cell count, differential white cell count), blood chemistry (plasma urea nitrogen, glucose, serum proteins, serum alkaline phosphatase, serum glutamic-pyruvic transaminase, serum glutamic-oxaloacetic transaminase, total cholesterol, whole blood specific gravity, serum electrolytes) or urinalysis (urinary volume, pH, specific gravity, protein, glucose, ketones, bile pigment, urobilinogen, blood pigments, electrolytes (Na, K, Mg, Ca)). There were no differences in the absolute mean organ weights including heart, liver, spleen, kidneys, adrenals and gonads. However, the relative mean kidney weight in the 4000 mg/kg/day groups was slightly heavier (non-statistically significant) than in the other dose groups. A statistically significant greater number of renal calcifications noted in female rats fed 2000 or 4000 mg/kg/day and the male rats fed 4000 mg/kg/day. This was considered a non-specific effect from changes in urine osmolarity rather than a direct effect of IMP. Nephrosis was noted in nearly all the rats from all the treated groups, but appeared to be more severe in the female rats fed 2000 or 4000 mg/kg/day and the male rats fed 4000 mg/kg/day (data not provided). Therefore, the authors report that the NOAEL in this rat study was 1000 mg/kg/day.

Yonetani *et al.* (1973) also studied the effects of IMP on Sprague-Dawley rats (N=14/group/sex) fed 0, 420, 880, 1790 or 3765 mg/kg/day IMP for 95 weeks. No significant changes were seen in mortality, behavior, body weight gain, food intake, hematology, blood chemistry or urinalysis. Histopathology revealed changes in several organs from all of the groups including controls, but the degree of changes were not treatment or dose related. Progressive glomerulonephritis was found in every rat in every group, including the control, with some differences in severity in the rats fed 3765 mg/kg/day IMP compared with the other treatment groups and control group. Thus, the NOAEL in this rat study was 1790 mg/kg/day.

Beagles (N=4/group/sex) were fed 0, 25, 250 or 500 mg/kg/day IMP for two years (Rivett *et al.*, 1972). No significant abnormalities were found clinically in body weight gain, food consumption or ophthalmoscopy. Hematology (erythrocyte sedimentation rate, packed cell volume, hemoglobin, reticulocyte count, mean corpuscular hemoglobin concentration, mean corpuscular volume, red cell count, white cell count, differential white cell count, platelet count, prothrombin time), biochemistry (plasma urea, plasma glucose, serum proteins, serum protein electrophoresis, albumin/globin ratio, serum alkaline phosphatase, serum glutamic-pyruvic transaminase, bilirubin, Na, K, allantoin, uric acid) and urinalysis (pH, volume, specific gravity, protein, glucose, ketones, bile pigments, bile salts, urobilinogen, microscopy of sediment) were normal. Macroscopic and microsopic examination of major organs (brain, heart, lungs, liver, pancreas, kidneys, spleen, gonads, prostate/uterus, thymus, thyroids, adrenals, pituitary) were normal. In addition, normal histopathology was noted for aorta (arch, abdominal), trachea, lymph nodes (cervical, mesenteric), gall bladder, urinary bladder, salivary gland, tongue, esophagus, stomach, duodenum, jejunum, ileum, colon, skin, mammary gland, skeletal muscle, bone marrow, peripheral nerve, eye and optic nerve. Small differences in serum allantoin levels were noted in dogs fed IMP, but this was not persistent nor dose related. The NOAEL in this dog study was 500 mg/kg/day, the highest dose tested.

**5.3.4. Studies on reproduction/teratogenicity**

Hashimoto *et al.* (1970) reported AMP (0, 5, 200, or 400 mg/kg/day) was not a teratogen when injected intraperitoneally during gestation days 7 – 13 (GD7-GD13) in ICR-JCL mice (N=20 litters) and SD-JCL rats (N=20-25 litters). There was slight (non-statistically significant growth retardation in fetuses, but no growth retardation was noted in the pups. The NOAEL in this mouse study was 400 mg/kg/day, the highest dose tested.

Palmer *et al.* (1971) conducted a three-generation reproduction study in rats (N=10M + 20F/group) fed 0, 250, 500 or 1000 mg/kg/day IMP. The rats were started on their test diets 60 days before mating. There were no effects on mating performance, pregnancy rate or duration of gestation. In male rats in all generations, body weight gain was greater in treated rats compared with controls. Litter size, pup weight, pup mortality and incidence of abnormalities were unaffected by treatment. Organ weight analysis, histopathology and skeletal staining of $F_{3B}$ pups revealed no consistent pattern related to treatment. The NOAEL in this rat study was 1000 mg/kg/day exposed during GD6-GD18, the highest dose tested.

Female Japanese white rabbits (N=13-18/group) were given 0, 200 or 2000 mg/kg/day IMP by gavage during gestation days 6-18 (GD6-GD18) (Jojima *et al.*, 1973). Four to five females of each group were delivered spontaneously and pups observed to day 30. All other dams were

killed at day 29 of gestation. No significant effects were noted on implantation sites, number of live or dead fetuses, body weight of live fetuses and external abnormalities. There was lower fetal mortality in the 200 mg/kg/day group compared to the control and high dose groups. All groups showed some delay in ossification, but no specific skeletal abnormalities were found that appeared to be due to IMP. The NOAEL in this rabbit study was 2000 mg/kg/day exposed during GD6-GD18.

### 5.3.5. Gene/DNA effects

AMP and adenine, with and without pre-incubation with liver extracts, tested negative for DNA-binding activity in Ehrlich ascites cells and *Escherichia coli* Q13 (Kubinski *et al.*, 1981). AMP (≤ 15 mM) prevented the mutation of *Salmonella typhimurium* (strain DG2670) and *E. coli* (strain DG1669) DNA when co-incubated with the mutagen, 9-aminoacridine (10 μg/ml) (Kopsidas and MacPhee, 1996).

### 5.3.6. Cell effects

Mitosis in human keratinocytes measured *in vitro* was reduced up to 59% compared with controls by treatment with 1 mM AMP (Flaxman and Harper, 1975; Harper *et al.*, 1974). There was no effect on the numbers of mitotic cells in the basal layer of mouse epidermis in adrenalectomized mice treated with 30 or 100 mg/kg AMP (no other details provided) (Vincent, 1973).

### 5.3.7. Observations in humans

Thirty-two adult patients were enrolled in a 28 day randomized, placebo controlled double-blind trial of AMP for the treatment of acute *Herpes zoster* (Sklar *et al.*, 1985). Treated patients (N=8M + 9F; 20 – 82 years) received by intramuscular injections 100 mg AMP in an aqueous gelatin base three times *per* week (~43 mg/day or 0.7 mg/kg/day for a 60 kg individual). Control patients (N=9M + 6F) received only aqueous gelatin base. Patients were evaluated at two-week intervals. There were no clinical signs of toxicity and cardiorespiratory function and blood pressures were normal. Clinical tests for complete blood cell counts, blood chemistry and urine evaluations were all normal. Gajdos (1974) reported the successful use of 160 – 200 mg/day oral AMP for greater than or equal to four weeks for the treatment of porphyria cutanea tarda.

The effects on uric acid levels from exposure to IMP was studied in healthy volunteers (N=3/group) given 0, 1.0, 1.5, 2.0 or 2.5 g/day IMP for 7 days (route not identified) (Copper *et al.*, 1972). Basal diet purine levels were maintained at 400 ± 40 mg/day throughout the experiment. Serum uric acid levels increased from 3.6 mg/dL in control group to 6.9 mg/dL in subjects receiving 2.5 g/day IMP (no other data provided). Uric acid 24-hour urinary excretion rate increased from 506 mg to 1100 mg in the control and 2.5 g/day groups, respectively (no other data provided). No side effects or toxic effects were reported observed.

Clifford *et al.* (1976) reported the acute effects from purine consumption, including AMP, on serum and urine uric acid levels in normouricemic (6.3 mg/dL; N=6; 45 years mean), hyperuricemic (8.5 mg/dL; N=11; 45 years mean) and gouty (8.3 mg/dL; N=8; 49 years mean) human male volunteers. Subjects were fed a low purine diet for 5 days prior to receiving a single

0.1 mmol/kg body weight oral dose of a single purine, AMP (2.1 g/person)[6] dissolved in fruit juice. Blood was drawn at 0, 2, 4, 6 and 8 hours and urine was collected 2 days prior to and 24 hours following treatment. Changes in uric acid were reported as the greatest difference observed between 0 hours and the time point (2, 4, 6 or 8 hours) with the highest measured uric acid level. Consumption of 2.1 g of AMP significantly elevated serum uric acid levels with a significantly greater increase observed in subjects with gout (+4.2 mg/dL) compared with hyperuricemic subjects (+1.9 mg/dL) and normouricemic controls (+2.2 mg/dL). Urinary uric acid output significantly increased 31%, 35% and 71% in the normouricemic, hyperuricemic and gouty subjects, respectively, but no significant differences were measured between the groups.

Waslien *et al.* (1968) fed healthy men (N=5/group; 21 - 38 years) 0, 2, 4 or 8 g/day yeast RNA equally distributed among four meals for 5 consecutive days. The basal diets contained egg albumin as the sole protein source and were therefore "purine free." Plasma and urinary uric acid increased linearly. At the end of the study, serum uric acid levels in subjects fed 0, 2, 4 or 8 g/day of yeast RNA (~0, 1, 2 or 4 g/day purine) were 4.9, 6.0, 7.7 and 9.4 mg/dL, respectively.

The effect of dietary protein level and yeast RNA on uric acid metabolism was studied in healthy men (N=6; mean age, 25 years) using a randomized block study protocol (Bowering *et al.*, 1970). Subjects lived in a metabolic unit for 60 days and were fed liquid diets providing daily nitrogen levels of 0.9 g (low-protein), 13 g (control), 62 g (high-protein) or 13 g nitrogen plus 4 g RNA (~2 g/day purine). There was a 1.7-fold increase in urine uric acid levels (1043 mg/day) in the group fed RNA compared to the control group (388 mg/day). Serum uric acid levels in the group fed RNA (9.2 mg/dL) were elevated by 0.8-fold compared to the control group (5.1 mg/dL). There was a ~25% increase in uric acid turnover time in the RNA group (1.3 days) compared to the control group (1.7 days).

The intravenous infusion of ATP for the treatment of advanced non-small cell lung cancer was studied in Phase I and Phase II clinical trials (Rapaport, 1993). Patients received ATP levels below those that affected arterial blood pressure (no other details provided). Toxicity and side effect profiles were characterized by minor cardiopulmonary events that were short lived and thought to be due to adenosine from ATP metabolism. Following consumption, AMP is thoroughly metabolized and would not be expected to cause any adverse cardiovascular responses. This is supported by the lack of any reported cardiovascular toxicity following oral AMP or other purine consumption.

## 6. RISK EVALUATION

AMP is ubiquitous to all living matter and the human diet. Purines have been continuously used as food additives in Japan prior to 1960. Purines and pyrimidines are approved food additives in Europe and are currently added to some infant formulas in the United States.

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[6] Based on a 60 kg individual.

JECFA has approved IMP as a food additive with the ADI not specified[7] and FEMA (No. 3669) has determined IMP as GRAS as a food ingredient.

AMP is rapidly and completely metabolized into uric acid in humans and into allantoin in all other non-primate mammals. The majority of evidence indicates that metabolism of AMP is complete prior to intestinal absorption. A study with AMP's initial metabolite, IMP, revealed a half-life of 5 hours and complete elimination, mainly in the urine, by 24 hours.

Adenosine induces physiological effects through binding to cell surface purinergic receptors. Intravenous adenosine administration causes vasodilation in the cardiovasculature, vasoconstriction in the kidneys and platelet aggregation. Inhalation of adenosine can induce asthma in asthmatics. These physiological responses have not been reported to occur following oral consumption of AMP. This is not surprising given that complete or near complete metabolism of AMP occurs following ingestion. Therefore, none of these non-oral adenosine-induced effects are considered relevant to assessing the risk from adding AMP to food.

Studies have reported that the free purine base, adenine, is nephrotoxic (reviewed in Warner, 1977). In rats, nephrotoxicity was observed after 14 days consumption of 420 mg/kg/day adenine (Story *et al.*, 1977). Mechanistic studies have identified that the kidney damage occurs from precipitation of the adenine metabolite, 2,8-dihyroxyadenine (2,8-DHA), in the renal tubules (reviewed in Bartlett, 1977). AMP and its initial metabolite, IMP, are not metabolized to 2,8-DHA, thus they would not cause similar renal toxicity. This fact is born out by the lack of treatment-dependent renal toxicity observed in multiple animal feeding studies using comparable or greater doses of nucleotide, including rats fed 1790 mg/kg/day of IMP for 95 weeks.

Subchronic animal studies with IMP have identified NOAELs ranging from 500 to 2000 mg/kg/day with an average of 1250 mg/kg/day. NOAELs for IMP from chronic studies ranged from 500 mg/kg/day (the highest dose tested) to a maximum of 1790 mg/kg/day in a 95-week study conducted in rats. AMP and IMP were not teratogenic or reproductive toxins in mice and rats (see Section 5.3.4).

Prolonged excessive purine consumption may lead to chronically elevated plasma uric acid levels (*i.e.*, hyperuricemia), which is one known risk factor for the development of gout. Gout is one of a group of disorders of purine metabolism resulting from deposition of uric acid crystals in the joints (Emmerson, 1996). Although the development of gout is thought to be related to hyperuricemia, the incidence of acute gout is only about 5 percent *per* year among patients with serum uric acid concentrations of 9.0 mg/dL and higher (Emmerson, 1996). The upper level of solubility of uric acid[8] in blood is considered to be ~7.0 mg/dL and normal serum

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[7]The statement "ADI not specified" means that, on the basis of the available data (toxicological, biochemical, and other), the total daily intake of the substance, arising from its use or uses at the levels necessary to achieve the desired effect and from its acceptable background in food, does not in the opinion of the Committee, represent a hazard to health. For this reason, and for the reasons stated in individual evaluations, the establishment of an acceptable daily intake (ADI) in mg/kg bw is not deemed necessary.

[8] Uric acid is the commonly used term, however, at physiological pH, 99% of uric acid is in the form of urate *i.e.*, the salt of uric acid. At pH less than 5.7, most of the molecules are in the form of uric acid (Emmerson, 1996).

uric acid levels in the U.S. have been reported to range between 4.0 to 7.5 mg/dL. The estimated average contribution to the serum uric acid levels in normal individuals from consumption of purines is approximately 1.4 mg/dL *per* gram purine consumed (Clifford *et al.*, 1976). In gouty individuals, serum uric acid levels increased twice as much *per* gram purine consumed compared with normal individuals giving an expected increase in serum uric acid levels of approximately 2.8 mg/dL *per* gram purine consumed. Thus, a conservative estimated change in serum uric acid levels from mean consumption of selected foods with added AMP (179 mg/day) would be an increase of 0.25 and 0.50 mg/dL in normal and gouty individuals, respectively. An increase of 0.50 mg/dL represents a possible maximum increase of 6.7% in individuals with gout at the high end of the normal range of serum uric acid (7.5 mg/dL). These small increases in serum uric acid levels from consumption of AMP are well within the standard deviation of the normal range in the U.S. population as well as the normal fluctuations in serum uric acid levels in individuals.

Humans and animals can consume large quantities of purines with little or no toxicity. The principal concern for purine consumption is the development of prolonged hyperuricemia, >7.0 mg/dL serum uric acid, which may lead to precipitation of uric acid in tissues. Based on regression equations established in human intervention studies, serum uric acid levels of 7.0 mg/dL would result from consumption of 1.83 g/day added purine in addition to the low levels (<11 mg/day) found in the study diets. Therefore, an acceptable daily intake (ADI) for total purine consumption in humans is 1800 mg/day. The current intake of purines in the human diet at the 90$^{th}$ percentile is 1120 mg day, leaving an ADI for AMP of 680 mg/day (*i.e.*, 1800 mg/day minus 1120 mg/day).

The mean and 90$^{th}$ percentile consumption of purines from all sources in the U.S. is estimated at 560 mg/day and 1120 mg/day, respectively. Addition of AMP to these foods at the levels indicated in Table 4 increases the estimated mean purine consumption to 709 mg/day and the 90$^{th}$ percentile consumption to 1427 mg/day. This theoretical intake level at the 90$^{th}$ percentile represents a conservative estimate and indicates that total purine consumption is within the ADI for total purines of 1800 mg/day and is therefore safe.

**(Remainder of page blank)**

## 7. CONCLUSION

After critically evaluating the information available, the Expert Panel has determined that, based on common knowledge throughout the scientific community knowledgeable about the safety of substances directly or indirectly added to food, there is reasonable certainty that AMP (Adenosine 5'-monophosphoric acid and its monosodium and disodium salts), produced and used in accordance with current Good Manufacturing Practice (cGMP), is safe under the intended conditions of use, and therefore is Generally Recognized As Safe (GRAS), by scientific procedures, when used as a food and beverage flavor enhancer (flavor modifier), so that total daily consumption of AMP, and its sodium salts, does not exceed 680 mg *per* day.

## 8. SIGNATURES

Joseph F. Borzelleca, Ph.D., F.A.T.S.
Medical College of Virginia

27 August 2003
Date

Walter H. Glinsmann, M.D.
Glinsmann Incorporated

8/26/03
Date

John A. Thomas, Ph.D., F.A.T.S.
Consultant

8/25/03
Date

## 9. REFERENCES


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## 10. APPENDIX 1 - Individual lots of AMP

**AMP, lot # B01P01N007**

**AMP, lot # B01P01N008**

**AMP, lot # B01P01N009**

**AMP, lot # B01P01N010**

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| | | | |
|---|---|---|---|
| mple #: | 03002422 | Finalized: | Mar 10 2003 |
| Received: | Mar 3 2003 | Print Date: | Mar 10 2003 |
| Description: | AMP | | |

DR. RICHARD BARNDT
LINGUAGEN CORP.
2005 EASTPARK BLVD
CRANBURY , NJ 08512-3515

| | |
|---|---|
| Client #: | 14660 |
| Phone: | 609-860-1500 |
| Fax: | 609-860-5900 |

## ANALYTICAL RESULTS

Results are representative of the sample(s) as submitted

| ANALYSIS | RESULT | UNIT | METHOD REFERENCE |
|---|---|---|---|
| Sample 1 *AMP, lot # B01P01N007* | | | |
| ESSENTIAL AMINO ACIDS | Passed | | AAP |
| BARIUM | <0.0001 | % | SW 6010 (FOODS) |
| COLOR | Passed | | NONE |
| LEAD | <0.50 | ppm | AOAC 986.15 |
| HEAVY METAL TOTAL | <0.50 | ppm (as Pb) | AOAC 986.15 |
| AMMONIA | Passed | as ammonium salts | EPA 350.3 |
| | 5.83 | | ION ACTIVITY |
| SPECIAL TESTING | Passed | Other nucleotides | NONE |

Tests were performed using the Food Chemicals Codex IV procedures for Disodium Inosinate.

Deviations from standardized methods: None unless otherwise noted.

Respectfully submitted for ABC Research

Kathy Barry
Manager, General Chemistry



000036

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Sample #: 03002830
Received: Mar 12 2003
Description: AMP

Finalized: Mar 18 2003
Print Date: Mar 18 2003

DR. RICHARD BARNDT
LINGUAGEN CORP.
2005 EASTPARK BLVD
CRANBURY , NJ 08512-3515

Client #: 14660
Phone: 609-860-1500
Fax: 609-860-5900

## ANALYTICAL RESULTS

Results are representative of the sample(s) as submitted

| ANALYSIS | RESULT | UNIT | METHOD REFERENCE |
|---|---|---|---|
| **Sample 1** *B01P01N008* | | | |
| ESSENTIAL AMINO ACIDS | Passed | | AAP |
| BARIUM | <0.0001 | % | SW 6010 (FOODS) |
| COLOR | Passed | | NONE |
| LEAD | <0.50 | ppm | AOAC 986.15 |
| HEAVY METAL TOTAL | <0.50 | ppm (as Pb) | AOAC 986.15 |
| AMMONIA | Passed | as ammonium salts | EPA 350.3 |
| [redacted] | 5.49 | | ION ACTIVITY |
| SPECIAL TESTING | Passed | Other nucleotidees | NONE |
| **Sample 2** *B01P01N009* | | | |
| ESSENTIAL AMINO ACIDS | Passed | | AAP |
| BARIUM | <0.0001 | % | SW 6010 (FOODS) |
| COLOR | Passed | | NONE |
| LEAD | <0.50 | ppm | AOAC 986.15 |
| HEAVY METAL TOTAL | <0.50 | ppm (as Pb) | AOAC 986.15 |
| AMMONIA | Passed | as ammonium salts | EPA 350.3 |
| PH | 5.72 | | ION ACTIVITY |
| SPECIAL TESTING | Passed | Other nucleotides | NONE |
| **Sample 3** *B01P01N010* | | | |
| ESSENTIAL AMINO ACIDS | Passed | | AAP |
| [redacted]IUM | <0.0001 | % | SW 6010 (FOODS) |
| COLOR | Passed | | NONE |

000037


Report Continues

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| | | | |
|---|---|---|---|
| mple #: | 03002830 | Finalized: | Mar 18 2003 |
| Received: | Mar 12 2003 | Print Date: | Mar 18 2003 |
| Description: | AMP | | |

DR. RICHARD BARNDT
LINGUAGEN CORP.
2005 EASTPARK BLVD
CRANBURY , NJ 08512-3515

| | |
|---|---|
| Client #: | 14660 |
| Phone: | 609-860-1500 |
| Fax: | 609-860-5900 |

## ANALYTICAL RESULTS

Results are representative of the sample(s) as submitted

| ANALYSIS | RESULT | UNIT | METHOD REFERENCE |
|---|---|---|---|
| Sample 3 *B01P01N010* | | | |
| LEAD | <0.50 | ppm | AOAC 986.15 |
| HEAVY METAL TOTAL | <0.50 | ppm (as Pb) | AOAC 986.15 |
| AMMONIA | Passed | as ammonium salts | EPA 350.3 |
| PH | 5.65 | | ION ACTIVITY |
| SPECIAL TESTING | Passed | Other nucleotides | NONE |

Tests were performed using the Food Chemicals Codex IV procedures for Disodium Inosinate.

Deviations from standardized methods: None unless otherwise noted.

Respectfully submitted for ABC Research

Kathy Barry
Manager, General Chemistry



000038

# CURRICULUM VITAE

# Joseph Francis Borzelleca

Personal History

Name: Joseph Francis Borzelleca
Address: Medical College of Virginia
States

S.S. No: upon request
Citizenship: United

Telephone:

Fax:

Email:

University Address: Dept. of Pharmacology and Toxicology
Medical College of Virginia
Virginia Commonwealth University
Box 980613
Richmond, VA 23298-0613

Educational Background

| | | |
|---|---|---|
| B.S. | St. Joseph's University, Philadelphia, PA<br>Biology, Chemistry | 1952 |
| M.S. | School of Graduate Studies<br>Thomas Jefferson University<br>Jefferson Medical College, Philadelphia, PA<br>Pharmacology, Physiology | 1954 |
| Ph.D. | School of Graduate Studies<br>Thomas Jefferson University<br>Jefferson Medical College, Philadelphia, PA.<br>Pharmacology, Biochemistry | 1956 |

Academic Appointments

| | | |
|---|---|---|
| Department of Pharmacology<br>Medical College of Pennsylvania<br>Philadelphia, PA | Instructor-Associate | 1956-1959 |
| Department of Pharmacology<br>and Toxicology<br>Medical College of Virginia<br>Richmond, VA 23298-0613 | Assistant Professor<br>Associate Professor<br>Professor<br>Head, Division of Toxicology<br>Professor Emeritus,<br>Pharmacology & Toxicology | 1959-1962<br>1962-1967<br>1967-<br>1972-1986<br>01 July 1996- |

Professional Certification

Fellow, Academy of Toxicological Sciences

Professional Affiliations

Societies

Academy of Toxicological Sciences* **
American Association for the Advancement of Science
American Chemical Society
American College of Toxicology*
American Society of Pharmacology and Experimental Therapeutics**
(Environmental Pharmacology Committee; Liaison Committee, SOT; Toxicology Committee)
Institute of Food Technologists (Professional Member)
International Society of Regulatory Toxicology and Pharmacology*
(Member of Council)
Sigma XI
Society of Experimental Biology and Medicine*
(Councilor; Program Chairman of Southeastern Section)
Society for RiskAnalysis
Society of Toxicology* **
(Member and/or Chairman: Awards, Education, Legislative Affairs, Membership, Nominating Committees; Secretary of the Society, Councilor, and President; President, Food Safety Specialty Section)
Virginia Academy of Science*
(Chairman, Medical Sciences Division)

* Held elected office
** Held appointed office or position

Board of Directors

ILSI (until 2002)

Board of Scientific and Policy Advisors

American Council on Science and Health (until 2000)

Journals

Editor, Food Chemical Toxicology, 1992-

Editorial Board
Environmental Carcinogenesis Reviews, 1981-
Journal of Environmental Pathology,Toxicology and Oncology 1977-
Journal of Environmental Science and Health, 1979-
Journal of the American College of Toxicology, 1982-
Journal of Toxicology: Cutaneous and Ocular Toxicology, 1982- 1992
Journal of Applied Toxicology, 1989-
Pharmacology, 1978-
Pharmacology and Drug Development, 1980-
Toxicology and Applied Pharmacology, 1975-1978

Consultantships (Past, Present)

Governmental

Food and Drug Administration
National Institute of Mental Health
National Cancer Institute
Environmental Protection Agency
Department of Labor - OSHA (Chairman, Carcinogens Standards Committee)
U.S. Army - Research and Development Command

Non-Governmental

National Academy of Sciences - NRC
Committee on Toxicology (Member, Chairman)/Board on Toxicology and Environmental Health Hazards
Safe Drinking Water Committee
Evaluation of Household Substances Committee (1138 Committee)
Food Protection Committee
Food Additives Survey Committee
Committee on Risk-Based Criteria for Non-RCRA Hazardous Wastes
Committee on Risk Assessment of Flame-Retardant Chemicals

Federation of American Societies of Experimental Biology
Select Committee on GRAS Substances
Flavors and Extracts
Biotechnology Product Safety
Caprenin GRAS Committee

World Health Organization
Joint Meeting on Pesticide Residues (JMPR) (Member, Chairman)

NATO/CCMS Drinking Water Committee

Industrial

Chemical Companies; Trade Associations

University Activities

Related to Instruction

Prepared a laboratory manual in pharmacology (animal and human studies) (1960)
Introduced the use of closed circuit TV and TV tapes in pharmacology (1960)
Introduced clinical pharmacological experiments into the medical and dental programs (1960)
Planning and participation in continuing education program (Schools of Dentistry, Medicine and Pharmacy)
Planning and administering each of the three major efforts in pharmacology (dental, medical, pharmacy) since 1960.
Graduate Program - assisted in developing graduate training program in toxicology

Current Teaching Activities

Presents lectures on Toxicological Issues, Food Intake and Control

Not Directly Related to Instruction

Elected senator from the graduate school, then vice-president of the University Senate
Served on various committees (e.g. Curriculum, Search, Animal Care, ) in each of the four major schools (Dentistry, Graduate, Medical, Pharmacy)

Research

Research was continuously funded from 1956. Sources of support included governmental (U.S.P.H.S.; N.I.H; E.P.A.; N.I.D.A.) and non-governmental (industrial). (A list of publications is attached).

Awards

DOD - US Army - Chemical Research Development and Engineering Center
Distinguished Service Award, 1986

National Italian - American Foundation Award
Excellence in Medicine and Community Service, 1987

Thomas Jefferson University
Distinguished Alumnus Award, 1987

Virginia Commonwealth University - School of Basic Health Sciences
Outstanding Faculty Award, 1987

Virginia Commonwealth University - School of Basic Health Sciences, Dept. of Pharmacology and Toxicology
Professor of the Year- 1992

American College of Toxicology
Distinguished Service Award- 1997

Virginia's Life Achievement in Science Award- April 2001

Bernard L. Oser Food Ingredient Safety Award by the Institute of Food Technologists- June 2001

International Society for Regulatory Toxicology and Pharmacology's International Achievement Award for 2001- December 2001

Society of Toxicology- Education Award- March 2002

PUBLICATIONS

Borzelleca, J.F. and Manthei, R.W.: Factors influencing pentobarbital sleeping time in mice. Arch. Int. Pharmacodyn. 111: 296, 1957.

Borzelleca, J.F.: Studies of the contribution of bladder absorption to the physiological changes induced by pentobarbital. J. Pharm. Exp. Ther.129: 305, 1960.

Borzelleca, J.F.: The absorption of nicotine from the urinary bladder of the dog. Arch. Int. Pharmacodyn. 133: 444, 1961.

Borzelleca, J.F., Bowman, E.R. and McKennis, H., Jr.: The cardiovascular and respiratory effects of (-)-cotinine. J. Pharmacol. Exp. Ther. 137: 313, 1962.

Borzelleca, J.F.: Drug absorption from the urinary tract of the rat. Nicotine. Arch.Int. Pharmacodyn. 143: 595, 1963.

Borzelleca, J.F.: Influence of saline and glucose infusions on the course of barbiturate intoxication. Arch. Int. Pharmacodyn. 146: 163, 1963.

Larson, P.S., Borzelleca, J.F., Bowman, E.R., Crawford, E.M., Smith, R.B., Jr. and Henningar, G.R.: Toxicologic studies on a preparation of p-tertiary octylphenoxy-polyethoxy ethanols (Trition X-405). Toxicol. Appl. Pharmacol. 5: 782, 1963.

Borzelleca, J.F., Larson, P.S., Henningar, G.R., Hug, E.G., Crawford, E.M. and Smith, R.B., Jr.: Studies on the chronic oral toxicity of monomeric ethyl acrylate and methyl methacrylate. Toxicol. Appl. Pharmacol. 6: 29, 1964.

Borzelleca, J.F. and Cherrick, H.: The excretion of drugs in saliva. Antibiotics. J. Oral Therap. Pharmacol. 2: 180, 1965.

Borzelleca, J.F. and Lester, D.: Acute toxicity of some perhalogenated acetones. Toxicol. Appl. Pharmacol. 7: 592, 1965.

Borzelleca, J.F.: Drug movement from the isolated urinary bladder of the rabbit. Arch. Int. Pharmacodyn. 154: 40, 1965.

Borzelleca, J.F.: Rabbit urinary bladder potentials. Invest. Urol. 3: 77, 1965.

Borzelleca, J.F.: Studies on the mechanisms of drug movement from the isolated urinary bladder. J. Pharmacol. Exp. Ther. 148: 111, 1965.

Lowenthal, W. and Borzelleca, J.F.: Drug absorption from the rectum. I. J. Pharm. Sci. 54: 1790, 1965.

Ambrose, A.M., Borzelleca, J.F., Larson, P.S., Smith, R.B., Jr. and Hennigar, G.R.: Toxicologic studies on monochloroacetaldehyde: 2,4-dinitrophenylhydrazone, a foliar fungicide. Toxicol. Appl.Pharmacol. 8: 472, 1966.

Borzelleca, J.F. and Doyle, C.H.: Excretion of drugs in saliva. Salicylate, barbiturate, sulfanilamide. J. Oral. Therap. Pharmacol. 3: 104, 1966.

Borzelleca, J.F. and Lowenthal, W.: Drug absorption from the rectum. II. J. Pharm. Sci. 55: 151, 1966.

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Evaluation of the health aspects of certain red and brown algae as food ingredients. 1973.

Evaluation of the health aspects of cellulose and certain cellulose derivatives of food ingredients. 1973.

Iodine in foods: chemical methodology and sources of iodine in the human diet. 1974.

Evaluation of the health aspects of aconitic acid as a food ingredient. 1974.

Evaluation of the health aspects of stannous chloride as a food ingredient. 1974.

Evaluation of the health aspects of licorice, glycyrrhiza and ammoniated glycrrhizin as food ingredients. 1974.

Evaluation of the health aspects of caprylic acid as a food ingredient. 1974.

Evaluation of the health aspects of sorbose as a food ingredient. 1974.

Evaluation of the health aspects of sulfuric acid and sulfates as food ingredients. 1974.

Evaluation of the health aspects of potassium iodide, potassium iodate, and calcium iodate as food ingredients. 1975.

Evaluation of the health aspects of dextran as food ingredients. 1975.

Evaluation of the health aspects of calcium oxide and calcium hydroxide as food ingredients. 1975.

Evaluation of the health aspects of succinic acid as a food ingredient. 1975.

Evaluation of the health aspects of certain calcium salts as food ingredients. 1975.

Evaluation of the health aspects of glycerin and glycerides as food ingredients 1975

Evaluation of the health aspects of dextrin and corn dextrin as food ingredients. 1975.

Evaluation of the health aspects of sodium thiosulfate as a food ingredient. 1975.

Evaluation of the health aspects of gelatin as a food ingredient. 1975.

Evaluation of the health aspects of bile salts and ox bile extract as food ingredients. 1975.

Evaluation of the health aspects of choline chloride and choline bitartrate as food ingredients.1975.

Evaluation of the health aspects of aluminum compounds as food ingredients. 1975.

Evaluation of the health aspects of tallow, hydrogenated tallow, stearic acid, and calcium stearate as food ingredients. 1975.

Evaluation of the health aspects of phosphates as food ingredients. 1975.

Evaluation of the health aspects of the tocopherols and a-tocopheryl acetate as food ingredients. 1975.

Evaluation of the health aspects of sorbic acid and its salts as food ingredients. 1975.

Evaluation of the health aspects of hydrogenated fish oil as a food ingredient. 1975.

Evaluation of the health aspects of beeswax (yellow or white) as a food ingredient. 1975.

Evaluation of the health aspects of inositol as a food ingredient. 1975.

Evaluation of the health aspects of malic acid as a food ingredient. 1975.

Evaluation of the health aspects of Japan Wax as a substance migrating to food from cotton or cotton fabrics used in dry food packaging. 1976.

Evaluation of the health aspects of carnauba wax as a food ingredient. 1976.

Evaluation of the health aspects of sulfamic acid as it may migrate to foods from packaging materials. 1976.

Evaluation of the health aspects of hydrosulfites as they may migrate to foods from packaging materials. 1976.

Evaluation of the health aspects of gum guaiac as a food ingredient. 1976.

Evaluation of the health aspects of tall oil as it may migrate to foods from packaging materials. 1976

Evaluation of the health aspects of corn sugar (dextrose), corn syrup and invert sugar as food ingredients. 1976.

Evaluation of the health aspects of sucrose as a food ingredient. 1976.

Evaluation of the health aspects of sulfiting agents as food ingredients. 1976.

Evaluation of the health aspects of glycerophosphates as food ingredients. 1976.

Evaluation of the health aspects of magnesium salts as food ingredients. 1976.

Evaluation of the health aspects of sodium hydroxide and potassium hydroxide as food ingredients. 1976.

Evaluation of the health aspects of adipic acid as a food ingredient. 1976.

Evaluation of the health aspects of hydrogenated soybean oil as a food ingredient.

Evaluation of the health aspects of formic acid, sodium formate, and ethyl formate as food ingredients. 1976.

Evaluation of the health aspects of lard and lard oil as they may migrate to foods from packaging materials. 1976.

Evaluation of the health aspects of pyridoxine and pyridoxine hydrochloride as food ingredients. 1977.

Evaluation of the health aspects of papain as a food ingredient. 1977.

Evaluation of the health aspects of hypophosphites as food ingredients. 1977.

Evaluation of the health aspects of coconut oil, peanut oil, and oleic acid as they migrate to food from packaging materials, and linoleic acid as a food ingredient. 1977.

Evaluation of the health aspects of pectin and pectinates as food ingredients. 1977.

Evaluation of the health aspects of tannic acid as a food ingredient. 1977.

Evaluation of the health aspects of rennet as a food ingredient. 1977.

Evaluation of the health aspects of acetic acid and sodium acetate as food ingredients. 1977.

Evaluation of the health aspects of sodium oleate and sodium palmitate as substances migrating to food from paper and paperboard used in food packaging. 1977.

Evaluation of the health aspects of corn silk as a food ingredient. 1977.

Evaluation of the health aspects of bentonite and clay (kaolin) as food ingredients.1977

Evaluation of the health aspects of citric acid, sodium citrate, potassium citrate, calcium citrate, ammonium citrate, triethyl citrate, isopropyl citrate, and stearyl citrate as food ingredients. 1977.

Evaluation of the health aspects of lactic acid and calcium lactate as food ingredients. 1978.

Evaluation of the health aspects of calcium pantothenate, sodium pantothenate, and D-pantothenyl acohol as food ingredients. 1978.

Evaluation of the health aspects of Vitamin B12 as a food ingredient. 1978.

Evaluation of the health aspects of Vitamin D2 and Vitamin D3 as food ingredients. 1978.

Evaluation of the health aspects of caffeine as a food ingredient. 1978.

Evaluation of the health aspects of certain glutamates as food ingredients. 1978.

Evaluation of the health aspects of protein hydrolyzates as food ingredients. 1978.

Evaluation of the health aspects of butylated hydroxyanisole as a food ingredient. 1978.

Evaluation of the health aspects of sodium, potassium, magnesium and zinc gluconates as food ingredients. 1978.

Evaluation of the health aspects of urea as a food ingredient. 1978.

Evaluation of the health aspects of thiamin hydrochloride and thiamin mononitrate as food ingredients. 1978.

Evaluation of the health aspects of biotin as a food ingredient. 1978.

Evaluation of the health aspects of ascorbic acid, sodium ascorbate, calcium ascorbate, erythorbic acid, sodium erythorbate, and ascorbyl palmitate as food ingredients. 1979.

Evaluation of the health aspects of propionic acid, calcium propionate, sodium propionate, dilauryl thiodipropionate, and thiodipropionic acid as food ingredients. 1979.

Evaluation of the health aspects of casein, sodium caseinate, and calcium caseinate as food ingredients. 1979.

Evaluation of the health aspects of nickel as a food ingredient. 1979

Evaluation of the health aspects of soy protein isolates as food ingredients. 1979.

Evaluation of the health aspects of carotene (B-carotene) as a food ingredient. 1979.

Evaluation of the health aspects of nitrogen, helium, propane, n-butane, isobutane, and nitrous oxide as gases used in foods. 1979.

Evaluation of the health aspects of hydrogen peroxide as a food ingredient. 1979.

Evaluation of the health aspects of riboflavin and riboflavin-5-1-phosphate as food ingredients. 1979.

Evaluation of the health aspects of starch and modified starches as food ingredients. 1979.
Evaluation of the health aspects of carbon dioxide as a food ingredient. 1979.

Evaluation of the health aspects of sodium chloride and potassium chloride as food ingredients. 1979.

Evaluation of the health aspects of certain silicates as food ingredients. 1979.

Evaluation of the health aspects of manganous salts as food ingredients. 1979.

Evaluation of the health aspects of copper gluconate, copper sulfate, and cuprous iodide as food ingredients. 1979.

Evaluation of the health aspects of hydrochloric acid as a food ingredient. 1979.

Evaluation of the health aspects of lecithin as a food ingredient. 1979.

Evaluation of the health aspects of potassium acid tartrate, sodium potassium tartrate, sodium tartrate and tartaric acid as food ingredients. 1979.

Evaluation of the health aspects of starter distillate and diacetyl as food ingredients. 1980.

Vitamin A, Vitamin A Acetate, and Vitamin A Palmitate as food ingredients. 1980.

Evaluation of the health aspects of iron and iron salts as food ingredients. 1980.

Evaluation of the health aspects of protein hydrolyzates as food ingredients. 1980.

Evaluation of the health aspects of collagen as a food ingredient. 1981.

Evaluation of the health aspects of methyl polysilicones as food ingredients. 1981.

Evaluation of the health aspects of soya fatty acid amines as food ingredients. 1981.

Evaluation of the health aspects of activated carbon (charcoal) as a food processing aid. 1981.

Evaluation of the health aspects of smoke flavoring solutions and smoked yeast flavoring as food ingredients. 1981.

Evaluation of the health aspects of cornmint oil as a food ingredient. 1981.

Evaluation of the health aspects of a mixture. Evaluation of the health aspects of diferrous, dipotassium ferrous, and potassium ferrocyanides as finding agents in wine production. 1981.

Evaluation of the health aspects of wheat gluten, corn gluten, and zein as food ingredients. 1981.

Evaluation of the health aspects of peptones as food ingredients. 1981.

Evaluation of the health aspects of shellac and shellac wax as food ingredients. 1981.

Evaluation of the health aspects of sodium metasilicate and sodium zinc metasilicate as food ingredients. 1981.

Evaluation of the health aspects of oat gum, okra gum, quince seed gum, and psyllium seed husk gum as food ingredients. 1982.

Contributing Authorship on the Following Publications of the National Academy of Sciences

Principles and Procedures for Evaluating the Toxicity of Household Substances.
Committee for the Revision of NAS Publication 1138, Committee on Toxicology, Assembly of Life Sciences, National Research Council, National Academy of Sciences
National Academy Press, Washington, D.C. 1977

Drinking Water and Health.
Safe Drinking Water Committee, Board on Toxicology and Environmental Health Hazards, Assembly of Life Sciences, National Research Council, National Academy of Sciences
Volume 1, 1977; Volume 2, 1980, Volume 3, 1980
National Academy Press, Washington, D.C.

Estimating Consumer Exposure to Food Additives and Monitoring Trends in Use.
Food Additives Survey Committee, Food and Nutrition Board, Institute of Medicine, National Academy of Sciences
National Academy Press, Washington, D.C. 1992

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Examination of Dietary Recommendations for Salt-Cured, Smoked, and Nitrite-Preserved Foods
Pariza, M.W., Borzelleca, J.F., Cassens, R.G., Filer, L.J., and Kritchevsky, D.,
CAST Issue Paper Number 8, November 1997

# WALTER H. GLINSMANN, M.D.

## EDUCATION

| | |
|---|---|
| 1956 | BA - Columbia College, New York, NY |
| 1960 | M.D. - Columbia College of Physicians and Surgeons, NY, NY |
| 1960-1965 | Internship and Residency in Medicine - New York Hospital (Cornell Medical School), NY, NY - Training at Dept, of Metabolism, Walter Read Army Medical Center and Army Institute of Research, Washington, DC |

## MEDICAL LICENSE

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| 1961-Current | New York State Physician, No. 086359. |

## EMPLOYMENT HISTORY:

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|---|---|
| 2002 | As below with change in academic affiliation: Fellow, Center for Food Safety and Nutrition and Ceres Forum®, Virginia Polytechnic Institute and State University (Virginia Tech), Alexandria, VA. Completed term as Scientific Advisor to Technical Committee, Life Sciences Institute. |
| 1998-2000 | President, Glinsmann, Inc. Evaluations of safety and health effects of foods, the development of nutritional products, and food-related claims.<br>Fellow and Adjunct Professor, Georgetown Center for Food and Nutrition Policy, Graduate School of Public Policy, Georgetown University.<br>Member, Expert Panel on Nutrition and Electrolytes, United States Pharmacopeial Convention, Inc.<br>Scientific Advisor to Technical Committee on Food Components for Health Promotion ("Functional Foods" or "Nutraceuticals") International Life Sciences Institute, North America and to U.S. and International Food Companies. |
| 1995-1997 | President, Glinsmann, Inc.<br>Fellow and Adjunct Professor, Georgetown Center for Food and Nutrition Policy, Graduate School of Public Policy, Georgetown University.<br>Advisor to the Committee on Revision (1995) and member, Expert Panel on Nutrition and Electrolytes, United States Pharmacopeial Convention, Inc. |

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Scientific Advisor to the Technical Committee on Food Components for Health Promotion, International Life Sciences Institute, North America. Expert Consultant, Office of the Deputy Director for Programs, Center for Food Safety and Applied Nutrition (CFSAN), U.S. Food and Drug Administration (FDA).

1993-1994 Expert in Nutrition, Office of Disease Prevention and Health Promotion, Office of the Assistant Secretary for Health, U.S. Department of Health and Human Services (DHHS). Provided management/technical support for nutrition and dietary guidance-related activities.

1992-1993 Visiting Fellow, Georgetown Center for Food and Nutrition Policy. Director, Nutrition Policy Staff, Office of Disease Prevention and Health Promotion, Office of the Assistant Secretary for Health, Public Health Service (PHS), DHHS, Provided leadership and coordination among DHHS agencies for Nutrition Policy Board functions; implementation of year 2000 nutrition objectives; development of dietary guidance with U.S. Department of Agriculture; and initiatives in food labeling, safety, and fortification: included program coordination for nutrition monitoring and related research; international nutrition conferences; interagency nutrition research initiatives; and preparation of nutrition and health reports and briefing materials.

1987-1991 Associate Director for Clinical Nutrition, Division of Nutrition, CFSAN, FDA. Provided program direction for human clinical and population-based research on: food safety; special dietary use and medical food products; novel food ingredients; health impacts of dietary behaviors of select populations; nutrient imbalances that relate to human morbidity and mortality; and techniques for assessing and monitoring nutritional status and adverse reactions to foods, food additives, and contaminants. Chaired the Center's Health Hazard Evaluation Board and Task Force for developing Guidelines for Clinical Testing for Food Additives and served as senior Center medical officer for developing Medical Foods Regulations. Represented Center or Agency interests and positions and provided guidance on human food safety evaluations to industry.

1983-1987 Chief, Clinical Nutrition Branch, Division of Nutrition, CFSAN, FDA. Developed and managed clinical nutrition activities, human food safety assessments, and the Nutrition Monitoring Program. Special assignments included: FDA Research in Human Subjects Committee; CFSAN Health Hazards Evaluation Board; primary responsibility for Center programs dealing with Clinical Nutrition, Clinical Investigations, Foods for Special Dietary Use, and Health-and Injury-Related Surveillance; Chairperson, Task Forces on Medical Foods Regulation and Evaluation of Health Aspects of Sugars Contained in Carbohydrate Sweeteners; and member Task Forces on Biotechnology, Food Monitoring Systems, and Nutrition and Toxicology Research Priorities.

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1978-1983 Chief, Experimental Nutritional Branch and Director of Research, Division of Nutrition, CFSAN, FDA. Developed, managed, conducted research based on CFSAN priorities; Special assignments included: FDA Research Involving Human Subjects Committee; Center/FDA Science Liaison; Center Health Hazards Evaluation Committee; and Task Forces on Nitrates-Nitrosamines, Research and Research Facilities Plans, Medical Foods Regulations, and Coordinated Use of Databases to Estimate Exposures.

1965-1978 Chief, Section on Physiological Controls, Laboratory of Biomedical Sciences, National Institute of Child Health and Human Development (NICHHD), National Institutes of Health (NIH), Bethesda, Maryland. Developed and managed research; Chief Intramural Research Contracts Officer (NICHHD); Institute Safety Officer; Member/Chair of Clinical Research Review and Grants and Contracts Review Committees.

1967-1968 Senior Research Investigator, Laboratory of Biomedical Sciences, NICHHD, NIH.

1966-1967 Guest Investigator, Clinical Endocrinology Branch, National Institute of Arthritis and Metabolic Diseases, NIH.

1965-1966 Medical Officer, Research Planning and Program Development, Growth and Development Program, NICHHD, NIH.

1962-1965 Assistant Chief, Department of Metabolism and Attending Physician in Medicine, Walter Reed Army Hospital, and Senior Investigator, Walter Reed Army Institute of Research, Washington, D.C.

## PROFESSIONAL MEMBERSHIPS

American Institute of Nutrition, renamed American Society for Nutritional Sciences (Membership Committee, 1986-1991, Fellow, 2002)
American Society for Clinical Nutrition (Membership Committee, 1986-1994: Chair, Publications Management Committee, American Journal of Clinical Nutrition, 1994-1996)
American Physiological Society
New York Academy of Sciences

## AWARDS

Fellow, American Society for Nutritional Sciences, 2002.

FDA Commendable Service Award: assessing safety and labeling of monosodium glutamate, 1999.

DHHS Secretary's Award for Excellence in Public Service, Implementing the Food Labeling Initiative, 1993.

PHS Citation for exemplary and creative work as a management clinician in nutrition research and investigative matters, 1989

FDA Award of Merit for Leadership, Health Hazard Evaluations, 1988

PHS Unit Commendation, Food Irradiation Safety Evaluation, 1988

PHS Citations for Outstanding Management Performance in Clinical Nutrition and Food Safety Evaluations, 1986-91

PHS Meritorious Service Medal for sustained high quality leadership and outstanding contributions to Nutrition and Food Safety, 1986

FDA Award of Merit for Leadership, Aspartame Clinical Investigation Team, 1986

FDA Commissioner's Special Citation to the Research Involving Human Subjects Committee for unique and outstanding performance to the Food and Drug Administration by promoting research while ensuring the protection of the human subjects involved, 1984

PHS Commendation Medal for sustained high quality leadership and professional accomplishments in planning, implementing, and evaluating nutrition research at the FDA

EXAMPLES OF SEMINARS, INVITED LECTURES

June 12, 2001 *Is There a Need for Cyclical Third Party Reviews? An Affirmative Assessment,*
10th Annual Conference, Functional Foods for Health, U. Illinois, Chicago, IL

April 29, 2001 *Orientation to Functional Foods*, Pediatric Academic Societies' Annual Meeting, Baltimore, MD

April 3, 2001 *Safety Regulation for Dietary Supplements: The System Needs a Significant Change* - Toxicology Roundtable, Experimental Biology, Orlando, FL

August 3, 2000 *Communicating Benefits to the Consumer: FTC, FDA, and Claim Substantiation*
Warner-Lambert-Pfizer Nutrition Symposium, Morris Plains, NJ

Jan. 27, 2000 *Concepts, Standards, and Substantiation of Effects of Functional Foods*
Workshop on Functional Foods, Kappel am Albis, Switzerland

June 14, 1999 *Scientific Concepts, Standards, and Substantiation*
American Association of Cereal Chemists Annual Meeting, Functional Foods – Strategies for the Food Industry, Newport Beach, CA

March 30,1999 *Distinguishing a Nutrient from a Drug*
Ceres Forum® on What is a Nutrient? Georgetown University Conference Center, Washington, DC

June 19, 1998 *The Role of Clinical Investigations in Establishing Safety and Efficacy for Functional Foods*
Course: A Global Perspective on Regulatory Approval for Food Ingredients, Nutraceuticals, and Dietary Supplements. Institute of Food Technologists Annual Meeting '98, Atlanta, GA

April 18, 1998 *Functional Foods: Regulatory Considerations*
Symposium: Functional Foods for Health Promotion: A Public Health Opportunity? Experimental Biology '98, San Francisco, CA

Oct. 27, 1997 *Functional Foods: Regulatory Considerations*
Panel: Are Consumers Ready for Functional Foods? American Dietetic Association Annual Meeting, Boston, MA

March 13, 1997 *Overview of Research on Health Benefits from Specific Phytochemicals*
Panel on Demystifying Functional Foods, Public Voice 20th Annual National Food Policy Conference, Washington, DC

Nov. 28, 1996 *Dietary Guidance and the U.S. Food Supply: Focus on Infants and Young Children*
Health Visitors Association Centenary Conference, Harrogate, England

Oct.17, 1996 *U.S. Health Claims: Rational and Lessons Learned*
Symposium on Health Claims for Foods in Canada, U. Toronto, Ontario, Canada

Feb. 26, 1996 *Statements of Nutritional Support: Claim Substantiation*
Symposium on the New Structure/Function Claims Frontier Under DSHEA, National Nutritional Foods Association, Washington, DC

Feb. 9, 1996 *Regulatory Framework: United States*
Workshop on Antioxidants, ILSI-Europe, Brussels, Belgium

Jan. 24, 1996 *Perspective on the Future of Designer and Functional Foods: Definitions, Regulatory Perspective, and Health Claims*
Annual Meeting, ILSI, Cancun, Mexico

Oct. 2, 1995
Oct. 3 *Food Labeling and Food Safety Requirements in the United States* and *International Developments in Food Fortification, Foods for Special Dietary Use, and Functional Foods*, Seminars, Doosan Technical Center, Seoul, Korea

Sept. 26, 1995 *Functional Foods in North America*
Sept. 28 *Regulatory Aspects of Functional Foods*
First International Conference on East-West Perspectives on Functional Foods, ILSI-Southeast Asia, Singapore

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PUBLICATIONS

Carpenter, M.B., Glinsmann, W.H., Fabrega, H. Effects of secondary striatal lesions upon cerebella dyskinesia. Neurology. 8: 352, 1958.

Carpenter, M.D., Fabrega, H., Glinsmann, W.H. Physiological deficits occurring with lesions of labyrinth and fastigial nuclei. J. Neurosphysiol. 22: 22, 1959.

Fiala, S., Glinsmann, W.H., Fiala, A.E. Deoxyribonucleotidase activity during carcinogenesis in rat liver. Naturwiss. 46: 635, 1959.

Swank, R.L., Glinsmann, W.H., Sloop, P. The production of fat embolism in rabbits by feeding high fat meals. Surgery, Gynecology and Obstetrics 110: 9, 1960.

Fiala, S., Fiala, A.E., Glinsmann, W.H. Deoxycytidylic deaminase in carcinogenic rat liver. Naturwiss, 47: 45, 1960.

Fiala, S., Glinsmann, W.H. Acid soluble ribonucleotides in adrenal tissue after hormonal stimulation. Endocrinology 68: 479, 1961.

Fiala, S., Fiala, A., Glinsmann, W.H. Mechanism of carcinogenesis and proliferation of tumor cells in rat liver. Pathologie-Biologie 9: 613, 1961.

Fiala, S., Glinsmann, W.H. A unified concept of cancerogenesis. Neoplasma 10: 1, 1963.

Glinsmann, W.H. Renal micropuncture studies during exsanguination hypotension. Clin. Res. 12: 252, 1964.

Ericsson, J.L.E., Glinsmann, W.H. Focal degenerative cytoplasmic alterations in liver cells induced by hypoxia. Electron microscopic observations. Acta Path. Microbial. Scand. 64: 151, 1965.

Ericsson, J.L.E., Glinsmann, W.H. Observations on the subcellar organization of hepatic parenchymal cells I. golgi apparatus, cytosomes, and cytosegresomes in normal cells. Lab. Invest. 15: 750, 1966.

Glinsmann, W.H., Ericsson, J.L.E. Observations on the subcellular organization of hepatic parenchymal cells II. Evolution of reversible alterations induced by hypoxia. Lab. invest. 15: 762, 1966.

Glinsmann, W.H., Mertz, W. Effect of trivalent chromium on glucose tolerance. Metabolism 15: 510, 1966.

Glinsmann, W.H., Feldman, F.J., Mertz, W. Plasma chromium during glucose loading. Science 152: 1243, 1966.

Mortimore, G., Mondon, C.E., King, E., Glinsmann, W.H. Effect of insulin on alterations in liver glycogen. Am. J. Physiol. 212: 179, 1967.

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Glinsmann, W.H., Mertz, W. Studies on the relationship between chromium and glucose tolerance in man. Proc. VIIth Internat. Cong. Nutrition, Vol. 5, p. 714, 1967.

Glinsmann, W.H., Mortimore, G.E. Influence of glucagon and 3', 5'-AMP on insulin responsiveness of the perfused rat liver. Am. J. Physiol. 216: 698, 1969

Glinsmann, W.H., Hern, E.P., Linarelli, L.G., Farese, R.V. Similarities between effects of adenosine 3', 5'-monophosphate and guanosine 3', 5'-monophosphate on liver and adrenal metabolism. Endocrinology 85: 711, 1969.

Farese, R.V., Linarelli, L.G., Glinsmann, W.H., Ditzion, B.R., Paul, M.I., Pauk, G.L. Persistence of the steroidogenic effect of adenosine-3', 5'-monophosphate in vitro: Evidence for a third factor during the steroidogenic effect of ACTH. Endocrinology 85: 867, 1969.

Linarelli, L.G., Weller, J.L., Glinsmann, W.H. Stimulation of fetal rat liver tyrosine aminotransferase activity in utero by 3', 5'-cyclic nucleotides. Life Sciences 9: 535, 1970.

Klein, D.C., Berg, G.R., Weller, J., Glinsmann, W.H. Pineal gland: dibutyryl cyclic adenosine monophosphate stimulation of labelled melatonin production. Science 167: 1738, 1970.

Glinsmann, W.H., Pauk, G., Hern E. Control of rat liver glycogen synthetase and phosphorylase activities by glucose. Biochem. Biophys. Res. Comm. 39: 774, 1970.

Berg, G., Glinsmann, W.H. Cyclic AMP in depression and mania. Lancet 1: 834, 1971.

Sherline, P., Lynch, A., Glinsmann, W.H. Cyclic AMP and adrenergic receptor control of rat liver glycogen metabolism. Endocrinology 91: 680, 1972.

Eisen, H.J., Glinsmann, W.H., Sherline, P. Effect of insulin on glycogen synthesis in fetal rat liver in organ culture. Endocrinology 92: 584, 1973.

Zieve, F.J., Glinsmann, W.H. Activation of glycogen synthetase and inactivation of phosphorylase kinase by a single phosphoprotein phosphatase. Biochem. Biophys. Res. Comm. 50: 872, 1973.

Eisen, H.J., Goldfine, I.E., Glinsmann, W.H. Regulation of hepatic glycogen synthesis during fetal development: roles for hydrocortisone, insulin receptors. Proc. Nat. Acad. Sci. (U.S.A.) 70: 759, 1973.

Sherline, P., Eisen, H., Glinsmann, W.H. Acute hormonal regulation of cyclic AMP content and glycogen phosphorylase activity in fetal liver in organ culture. Endocrinology 94: 935, 1974.

Glinsmann, W.H., Eisen, H.J., Lynch, A., Chez, R.A. Glucose regulation by isolated near-term fetal monkey liver. Pediat. Res. 9: 600, 1975.

Eisen, H.J., Glinsmann, W.H. Partial purification of glucocorticoid receptor from rat liver using DNA-cellulose. J. Steroid Biochem. 6: 1171, 1975.
Huang, K. P., Huang, F.F., Glinsmann, W.H., Robinson, J.C. Regulation of glycogen synthetase activity by two kinases. Biochem. Biophys. Res. comm. 65: 1163, 1975.

Huang, F.L., Glinsmann, W.H. Inactivation of rabbit muscle phosphorylase phosphatase by cyclic AMP-dependent kinase. Proc. Nat. Acad. Sci. (U.S.A.) 72: 3004, 1975.

Sparks, J.W., Lynch A., Glinsmann, W.H. Regulation of rat liver glycogen synthesis and activities of glycogen cycle enzymes by glucose and galactose. Metabolism 25: 47, 1976.

Sparks, J.W., Lynch A., Chez, R.A., Glinsmann, W.H. Glycogen regulation in isolated perfused near-term monkey liver. Pediat. Res. 10: 51, 1976.

Huang, F.L., Glinsmann, W.H. A second heat-stable protein inhibitor of phosphorylase phosphatase from rabbit muscle. FEBS Lett. 62: 326, 1976.

Eisen, H.J., Glinsmann, W.H. Partial purification of the glucocorticoid receptor from rat liver: a rapid two-step procedure using DNA-cellulose. Biochem, Biophys, Res. Comm. 70: 367, 1976.

Huang, K. P., Huang, F.L., Glinsmann, W.H., Robinson, J.C. Effect of limited proteolysis on activity and phosphorylation of rabbit muscle glycogen synthetase. Arch. Biochem. Biophys. 173: 6, 1976.

Huang, F.L., Glinsmann, W.H. Separation and characterization of two phosphorylase phosphatase inhibitors from rabbit skeletal muscle. European J. Biochem. 70: 419, 1976.

Nakai, C., Glinsmann, W.H. Effects of polyamines on nucleosidediphosphate kinase activity. Biochem. Biosphys. Res. Comm. 74: 1419, 1977.

Nakai, C., Glinsmann, W.H. Inhibition of rabbit skeletal muscle phosphorylase phosphatase by spermine. Molec. Cellular Biochem. 15: 141, 1977.

Nakai, C., Glinsmann, W.H. Protein inhibitors of phosphorylase phosphatase and cyclic AMP-dependent protein kinase from rabbit muscle. Molec. Cellular Biochem. 15: 133, 1977.

Glinsmann, W.H., Huang, F.L., Tao, S., Nakai, C. Control of rabbit muscle phosphorylase phosphatase activity. Proc. FEBS Congress, Copenhagen. Elsevier Press, 1977.

Huang, F., Tao, S., Glinsmann, W.H. Multiple forms of protein phosphatase inhibitors in mammalian tissues. Biochem. Biophys. Res. Comm. 78: 615, 1977.

Eisen, H.J., Glinsmann, W.H. Maximizing purification of the activated glucocorticoid receptor by DNA-cellulose chromatography. The Biochem. J., Molecular Aspects, 17: 1977.

Nakai, C., Glinsmann, W.H. Interaction between polyamines and nucleotides. Biochemistry 16: 5636, 1977.

Buffone, G.J., Sparks, J.W., Johnson, J., Iosefsdin, M., Lewis, S.A., Glinsmann, W.H. Evaluation of an immobilized enzyme electrode system for the monitoring of therapeutic galactose concentrations in neonates. Clin. Chem. 23: 1166, 1977.

Tao, S.H., Huang, F.L., Lynch, A., Glinsmann, W.H. Control of rat skeletal muscle phosphorylase activity by adrenalin. Biochem. J. 176: 347, 1978.

Simpkins, R.A., Eisen, H.J., Sparks, J.W., Glinsmann, W.H. Development of gluconeogenesis from galactose by fetal liver explants in organ culture. Devel. Biol. 66: 353, 1978.

Simpkins, R.A., Eisen, H.J., Glinsmann, W.H. Functional integrity of fetal rat liver explants cultured in a chemically defined medium. Devel. Biol. 66: 344, 1978.

Sparks, J.W., Avery, G.B., Fletcher, A.B., Simmons, M.A., Glinsmann, W.H. Parenteral galactose therapy in the glucose-intolerant premature infant. The J. of Pediatrics 100: 255, 1982.

Anderson, R.A., Polansky, M.M., Bryden, N.A., Roginski, E.E., Patterson, K.Y., Veillon, C., Glinsmann, W.H. Urinary chromium excretion of human subjects; effects of chromium supplementation and glucose loading. Amer. J. Clin. Nutr. 36: 1184, 1982.

Anderson, R.A., Polansky, M.M., Bryden, N.A., Roginski, E.E., Mertz, W., and Glinsmann, W.H. Chromium supplementation of human subjects: effects on glucose, insulin, and lipid variables. Metabolism 32: 894, 1983.

Anderson, R.A., Polansky, M.M., Bryden, N.A., Patterson, K.Y., Veillon, C., Glinsmann, W.H. Effects of chromium supplementation on urinary Cr excretion of human subjects and correlation of Cr excretion with selected clinical parameters. J. Nutr. 113: 276, 1983.

Yetley, E.A., Glinsmann, W.H. Regulatory issues regarding iron bioavailability. Food Technol. 37: 121, 1983.

Archer, D.L., Glinsmann, W.H. Hypothesis: Intestinal infection and malnutrition initiate acquired immune deficiency syndrome (AIDS). Nutrition Research 5: 9, 1985.

Archer, D.L., Glinsmann, W.H. Enteric infections and other co-factors in AIDS: Possible intervention points from a historical perspective. Immunology Today 6: 292, 1985.

Glinsmann, W.H., Irausquin, H., Park, Y.K. Evaluation of health aspects of sugars contained in carbohydrate sweeteners; report of task force 1986. J. Nutr. 116 - supplement 11: S1-216, 1986.

Glinsmann, W.H., Tollefson, L.K., Hattan, D.G. Evaluation of adverse reactions reported to be associated with the use of aspartame-containing products. *Proc. International Aspartame Workshop*, Ed. P.B. Dews. Publ. Int'l Life Sci. Inst. - Nutr. Found., Washington, D.C., 1987.

Tollefson, L.K., Barnard, R.J., Glinsmann, W.H. Monitoring of adverse reactions to aspartame. Proc. *First International Meeting on Dietary Phenylalanine and Brain Function.* Ed. R.J. Wurtman and E. Ritter-Walker, p. 347-72, Publ. Ctr. for Brain Sciences and Metabolism Charitable Trust, Cambridge, Massachusetts, 1987.

Glinsmann, W.H., L.K. Tollefson, Park, Y.K. Regulatory status and health aspects of sweeteners. In *Sweeteners: Health Effects*, Ed. G.M. Williams, p. 263-74, Princeton Sci. Publ. Inc., Princeton, New Jersey, 1988.

Glinsmann, W.H., Dennis, D.A. Regulation of nonnutritive sweeteners and other sugar substitutes. In *Sweeteners*, Eds. N. Kretchmer and C. Hollenbeck, p. 257-85, CRC Press, Boca Raton, Florida, 1991.

Glinsmann, W.H. Usefulness of clinical studies in establishing safety of food products. In *ACS Symposium Series, No 484, Food Safety Assessment*, Eds. J.W. Finley, S.F. Robinson, and D.J. Armstrong, p. 105-13, Amer. Chem. Society, 1992.

Vanderveen, J.E., Glinsmann, W.H. Fat substitutes: a regulatory perspective. In Ann. Rev. Nutr., Vol. 12, Eds. R.E. Olsen, D.M. Bier, and D.B. McCormick, p. 473-87, Annual Reviews Inc., Palo Alto, California, 1992.

*Workshop on Dietary Fatty Acids and Thrombosis*, March 1991, Proceedings Eds. J.C. Hoak, W.H. Glinsmann, J.T. Judd. Amer. J. Clin. Nutr. 56 - supplement 4: 7835-8265, 1992.

Hyman, F.N., Sempos, E., Saltsman, J., Glinsmann, W.H. Evidence for success of caloric restriction in weight loss and control: summary of data from industry. *NIH Technology Assessment Conference on Methods for Voluntary Weight Loss and Control.* Ann. Int. Med. 119: 681-87, 1993.

Glinsmann, W.H., Bowman, B. Public health significance of dietary fructose. In *Health Effects of Dietary Fructose*, Eds. A.L. Forbes and B.A. Bowman. Amer. J. Clin. Nutr. 58 - Supplement 5:820-23, 1993.

Glinsmann, W.H., Park, Y.K. Perspective on the 1986 FDA assessment of the safety of carbohydrate sweeteners; uniform definitions and recommendations for future assessments. Amer. J. Clin. Nutr. 62 (suppl): 161S-9S, 1995.

Shank, F.R., Carson, K., Glinsmann, W.H. Putting things in perspective: building on our experience. (1995 Ceres Forum: *Fortifying Policy with Science - The Case for Folate*) J. Nutrition 126 (suppl): 781-87S, 1996.

Glinsmann, W. Focus on substitutes that alter gastrointestinal physiology. (*Proceedings of the Workshop on Safety and Regulatory Aspects of Macronutrient Substitutes,* Nov. 1994, Washington, D.C.) Regulatory Toxicol. and Phamacol. 23(suppl): S27-30, 1996.

Glinsmann, W. H., Bartholmay, S.J., Coletta, F. Dietary guidelines for infants: a timely reminder. Nutrition Reviews 54:50-57, 1996.

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Glinsmann, W.H. Functional foods in North America. In *Proceedings of First International Conference on Functional Foods*, Singapore, September 1995. Eds. F.M. Clydesdale and S.H. Chan. Nutrition Reviews, Vol. 54, No. 11, Part II, S33-37, 1996.

Glinsmann, W.H. Perspective on functional food development and commercialization. J. Nutraceuticals, Functional & Medical Foods, 1:89-93, 1997.

Glinsmann, W.H. Functional foods: an overview of regulatory status. Nutrition Today, 34:1-4, 1999.

Glinsmann, W. Functional Foods: Special Considerations in the Pediatric Diet. Pediatric Basics, 92:2-15, 2000.

Flamm, G., Glinsmann, W., Kritchevsky, D., Prosky, L., Roberfroid, M. Inulin and oligofructose as dietary fiber: A review of the evidence. Critical Reviews in Food Science Nutrition, 41:353-62, 2001.

Campbell, E., Glinsmann, W., Rheinhardt, W., Claims regarding the health benefits of foods. Nutrition and the M.D., 28:1-5, 2002.

CURRICULUM VITAE

John A. Thomas, Ph.D.

**WORK HISTORY SUMMARY**

| | |
|---|---|
| 1961-1982 | PROFESSORSHIPS, PHARMACOLOGY& TOXICOLOGY University of Iowa & University of Virginia, Creighton University, and West Virginia University |
| 1972-1982 | DEANSHIPS, SCHOOL OF MEDICINE, Morgantown, WV Associate Dean, West Virginia University Assistant Dean, West Virginia University |
| 1982-1987 | VICE PRESIDENT, CORPORATE RESEARCH, BAXTER HEALTHCARE, Deerfield, IL (Multi-National Health Care Corporation) |
| 1988-1999 | VICE PRESIDENT, ACADEMIC SERVICES University of Texas Health Science Center, San Antonio, Texas(UTHSCSA) |
| 1988-Present | PROFESSORSHIP, PHARMACOLOGY (Emeritus, 1999) University of Texas Health Science Center, San Antonio, Texas |

**PERSONAL**

**MILITARY SERVICE**

| | |
|---|---|
| 1953-1955 | Noncommissioned Officer (Sergeant) U.S. Army |

**EDUCATION**

| | |
|---|---|
| 1938-1950 | La Crosse Public Schools, La Crosse, Wisconsin |
| 1951-1953<br>1955-1956 | University of Wisconsin, La Crosse, Wisconsin |
| 1956-1961 | University of Iowa, Iowa City, Iowa |

**ACADEMIC DEGREES**

| | |
|---|---|
| 1956 | B.S., University of Wisconsin |
| 1958 | M A., University of Iowa |
| 1961 | Ph.D., University of Iowa |

## RECENT/CURRENT ACADEMIC APPOINTMENTS

| | |
|---|---|
| Professor Emeritus | Department of Pharmacology, University of Texas Health Science Center San Antonio, TX |
| Professor | Department of Obstetrics/Gynecology, University of Texas Health Science Center, San Antonio, TX |
| Adjunct Professor | Environmental Sciences School of Public Health, University of Texas - Houston |
| Clinical Professor | Division of Pharmacology & Toxicology College of Pharmacy, University of Texas – Austin (2000-present) |

## LICENSES AND CERTIFICATES

| | |
|---|---|
| 1957 | American Registry of Physical Therapists (Inactive) |
| 1982-1988 | American Academy of Toxicological Sciences - Diplomate |
| 1988-1998 | American Academy of Toxicological Sciences - Diplomate (re-certified) |
| 1997-2002 | American Academy of Toxicological Sciences - Diplomate (re-certified) |
| 2002-2007 | American Academy of Toxicological Sciences – Diplomate(re-certified) |

## HONORS AND PROFESSIONAL RECOGNITION

| | |
|---|---|
| 1960-1966 | Dean's Lists, University of Wisconsin - La Crosse; Gamma Alpha, Science Honorary, University of Iowa Pre-doctoral Fellowships, University of Iowa; Foreign Travel Award, American Society for Pharmacology and Experimental Therapeutics, Mexico City, Mexico & Sao Paulo, Brazil |
| 1968 | Chairman Endocrine Pharmacology, American Society for Pharmacology and Experimental Therapeutics (University of Minnesota) |
| 1971 | Chairman, Endocrine Pharmacology, Federation of American Society for Experimental Biology (Atlantic City, NJ) |
| | Visiting Professor and Senior Research Advisor, Faculty of Medicine, University of Ottawa, Ontario, Canada |
| | McLaughlin Award - Outstanding Teaching Award, West Virginia University School of Medicine (Shared Award) Elected |
| | Fellow, American School Health Association |
| 1973 | Co-Chairman, Liver Microsomal Enzymes, Society for Toxicology NY |
| 1973-1974 | Outstanding Teaching Award, West Virginia University |
| 1974 | Co-Chairman, Endocrine Pharmacology, American Society of Pharmacology and Experimental Therapeutics (University of Montreal) |

**HONORS AND PROFESSIONAL RECOGNITION (Cont'd)**

| | |
|---|---|
| 1975-1982 | Adjunct Professor, Department of Allied Health Sciences, Kent State University |
| 1975 | Co-Chairman, Endocrine Pharmacology, American Society for Pharmacology and Experimental Therapeutics (University of California Davis) |
| 1977 | U.S. Environmental Protection Agency - Certificate of Scientific Service |
| 1977 | McLaughlin Award - Outstanding Teaching Award, West Virginia University School of Medicine (Shared Award) |
| 1978 | American Men & Women in Science |
| 1978 | National Academy of Science Travel Award, Xii International Cancer Congress, Buenos Aires, Argentina |
| 1978 | Maurice 0. Graff Distinguished Alumni Award (University of Wisconsin - La Crosse) |
| 1980 | Co-Organizer, N.I.E.H.S.-Sponsored Target Organ Toxicity: The Endocrines (West Virginia University) |
| 1980 | Moderator, Environmental Effects on Maturation, Cold Springs Harbor, NY |
| 1981 | Who's Who in Health Care, 2nd edit. |
| 1980-1982 | Director, Target Organ Toxicity, Inc., Raleigh, NC |
| 1982 | Organizer, American Society Pharmacology & Experimental Therapeutics/ Society of Toxicology.-Sponsored Symposium, Innovating Models in Teratogenicity (University of Louisville) |
| 1983 | Organizer, Society of Toxicology, Workshop on Male Reproductive Toxicology, Las Vegas, Nevada |
| 1983 | Marquis Who's Who (Science & Technology) |
| 1984 | Co-Recipient, Association of American Publications Award (Technical, Scientific & Scholarly Division). American Journal of Industrial Medicine |
| 1984 | Secretariat, Scientific Organizing Committee, International Conference on Phthalate Acid Esters, IX IUPHARM Congress, University of Surrey, U.K. |
| 1984 | Elected Fellow, American Academy of Veterinary Pharmacology & Therapeutics |
| 1985 | Moderator/Organizer, Monoclonal Antibodies: Their Use in Toxicology & Pharmacology, Society of Toxicology Refresher Course, San Diego, CA |
| 1985 | Chairman/Organizer, Male Reproductive Toxicology, American College of Toxicology, Washington, DC |

**HONORS AND PROFESSIONAL RECOGNITION (Cont'd)**

| | |
|---|---|
| 1985 | Marquis Who's Who in the Midwest, 20th Edition |
| 1985 | Chairman, Plant Biotechnology Consortium Workshop - Pharmaceuticals, Chicago, IL |
| 1985-1987 | Councilor, Society of Toxicology |
| 1986-1988 | Councilor, American College of Toxicology |
| 1986 | Midwest Toxicology Society, President-elect |
| 1986 | Chairman, FASEB Symposium, New Drugs Through Biotechnology, St. Louis, MO |
| 1986 | Organizer, Gordon Conference, Basic Mechanisms of Gonadal Toxins, NH |
| 1986 | Distinguished Visiting Professor, Department of Chemistry, University of Wisconsin, La Crosse, WI |
| 1986 | Kenneth P. DuBois Award, Outstanding Achievement in Toxicology, Midwest Region, Society of Toxicology |
| 1986-1993 | Board of Directors, University of Wisconsin Foundation, La Crosse, WI |
| 1987 | Vice Chairman, Gordon Conference, Mechanisms of Toxicity, NH |
| 1987 | Chairman, Society of Toxicology, Symposium on rDNA-Derived Proteins: Toxicologic Considerations, San Diego, CA |
| 1987 | Distinguished AMA Lecturer in Medical Sciences, American Medical Association, Chicago, IL |
| 1987 | Co-Chairman, American Chemical Society, Occupational Hazards Symposia, Denver, CO |
| 1987 | Vice President - Midwest Toxicology Society |
| 1988 | Chairman, Society of Toxicology, Endocrine Toxicology, Dallas, TX |
| 1988 | President - Midwest Toxicology Society |
| 1989 | Chairman, Gordon Research Conference, Mechanisms of Toxicity, NH |
| 1989-1999 | Board of Scientific Advisors, Texas Society of Biomedical Research |
| 1990 | President, American Chem. Society, Sub-Division of Chemical Pathology & Toxicology |
| 1990 | Fellow, American Academy of Toxicology Sciences |
| 1991 | Who's Who in Education |
| 1992 | Who's Who, Environmental Registry |
| 1994-2000 | Trustee, International Life Sciences Institute (ILSI) North America |
| 1995 | Vice President, American College of Toxicology |

**HONORS AND PROFESSIONAL RECOGNITION (Cont'd)**

| | |
|---|---|
| 1995-Elected | Russian Academy of Medical Sciences, Foreign Member |
| 1995 | Secretary, Gulf State Chapter, Society of Toxicology |
| 1996 | Vice President, Gulf State Chapter, Society of Toxicology |
| 1996 | Honorary member, Scientific Council, Moscow Medical & Stomatological Instit. |
| 1996 | President-Elect, American College of Toxicology |
| 1996 - 2001 | Board of Directors, Academy of Toxicological Sciences |
| 1997 | President, American College of Toxicology |
| 1997 | Distinguished Alumni Award-Achievement, University of Iowa |
| 1997 | Vice President, Texas Society for Biomedical Research |
| 1997 - 2002 | Member Expert Advisory Panel, Canadian Network of Toxicology Centers |
| 1998 -1999 | President, Gulf State Chapter, Society of Toxicology |
| 1998 | Merit Award (Distinguished Career), Society of Toxicology |
| 1999 | Who's Who in Medicine & Healthcare, 2nd ed, 1999-2000, 3rd ed. 2001 |
| 1999 | Distinguished Service Award, American College of Toxicology |
| 1999 | Vice President, Academy of Toxicologic Sciences |
| 2000 | President, Academy of Toxicologic Sciences |
| 2001-2003 | Marquis' Who's Who in the South and Southeast |
| 2002 | Marquis' Who's Who in Medicine & Healthcare, 4th edit. |

**PROFESSIONAL SOCIETY COMMITTEES**

| | |
|---|---|
| 1973-1983 | Amer. Soc. Pharmacol. & Exper. Therap., Committee on Environ. Pharmacol. |
| 1980-1982 | ASPET - Section on Toxicology |
| 1982-1983 | Society of Toxicology, Education Committee |
| 1984-1986 | Midwest Toxicology Society, Secretary |
| 1985 | Awards Committee, ASPET |
| 1986-1988 | Program Committee, American College of Toxicology |
| 1988-1991 | Executive Committee, ASPET - Section on Toxicology |

**PROFESSIONAL SOCIETY COMMITTEES (Cont'd)**

| | |
|---|---|
| 1993 | Program Committee, Society for Basic Urologic Research |
| 1993 | Chair, Environmental and Toxic Exposures in Epidemiology of Neural Tube Defects, International Conference on Neural Tube Defects |
| 1993-1997 | Member, National Library of Medicine (LSTRC) |
| 1993-1994 | International Conference on Neural Tube Defects, Organizing Committee, Harlingen, TX |
| 1994-1997 | Executive Committee, Division of Toxicology, ASPET. |
| 1993-2000 | Trustee, International Life Sciences Institute (ILSI) N.A. |
| 1997 | Publication's Committee, American College of Toxicology |
| 1997-2000 | Chair, Expert Advisory Panel, Canadian Network Toxicology Centers |
| 1998 | Vice-Chairman, Scientific Program, International Life Sciences Institute (ILSI) |
| 1999 | Chairman, Scientific Program, International Life Sciences Institute (ILSI) |
| 1998-2000 | Education Committee, Society of Toxicology (Chair, 2000) |
| 1998 | Member, American Conference of Governmental Industrial Hygienists |
| 1999-2002 | Member, IOM/NAS, Subcommittee on Micronutrients, Re-appointed, 2002-04 |

**RESEARCH APPOINTMENTS**

| | |
|---|---|
| 1958-1959 | Research Associate, University of Iowa |
| 1982 | Visiting Senior Scientist - Travenol Laboratories, Chicago, IL |
| 1982-1988 | Research Professor, Department of Urology, Northwestern University School of Medicine |

**TEACHING ASSISTANTSHIPS AND/OR ACADEMIC APPOINTMENTS**

| | |
|---|---|
| 1960 | Teaching Assistant, Department of Physiology, School of Medicine, University of Iowa |
| 1961 | Instructor, Department of Physiology, School of Medicine, University of Iowa |
| 1961-1964 | Assistant Professor, Department of Pharmacology, University of Virginia School of Medicine |
| 1964-1967 | Associate Professor, Department of Physiology- Pharmacology, Creighton University School of Medicine |

**TEACHING ASSISTANTSHIPS AND/OR ACADEMIC APPOINTMENTS (Cont'd)**

| | |
|---|---|
| 1967-1969 | Associate Professor, Department of Pharmacology, West Virginia University School of Medicine |
| 1970 | Visiting Professor and Acting Chairman, Department of Pharmacology, Pahlavi University School of Medicine, Shiraz, Iran (University of Pennsylvania exchange program) |
| 1970-1982 | Professor, Department of Pharmacology and Toxicology, West Virginia University School of Medicine, Morgantown, WV |
| 1982-1988 | Instructor (Adjunct), Department of Pharmacology, Rush Medical College, Chicago, IL |
| 1982-1988 | Lecturer (Adjunct), Department of Pharmacology and Toxicology, University of Illinois School of Medicine, Chicago, IL |
| 1986-1988 | Professor (Adjunct), Division of Clinical Pharmacology, University Health Science/Chicago Medical School, North Chicago, IL |
| 1982-1991 | Professor (Adjunct), Department of Pharmacology and Toxicology, West Virginia University School of Medicine, Morgantown, WV |
| 1982-Present | Professor (Adjunct), Department of Pharmacology & Toxicology, Northwestern University School of Medicine, Chicago, IL |
| 1986-Present | Clinical Professor (Adjunct), Department of Preventive Medicine, Medical College of Wisconsin, Milwaukee, W |
| 1977 | Clinical Professor, The University of Texas School of Pharmacy |
| 1987 | Adjunct Professor, Department of Environmental Sciences, University of Texas School of Public Health |
| 1988-1998 | Professor, Department of Pharmacology, University of Texas Health Science Center, San Antonio, TX |
| 1988-1998 | Professor, Department of Obstetrics/Gynecology, University of Texas Health Science Center, San Antonio, TX |
| 1999 | Professor, emeritus, Department of Pharmacology, The University of Texas Health Science Center, San Antonio, TX |

**RESEARCH ACTIVITIES/INTERESTS**

- Prostate Biochemistry/Pathology; Steroid Receptors
- Reproductive System Toxicity
- Drug-Hormone Interactions
- Toxicology of Industrial Chemicals
- Environmental & Occupational Toxicology
- New Drugs Through Genetic Engineering

**ORGANIZATIONS (Past and Present)**

- American Society for Pharmacology and Experimental Therapeutics (ASPET)
- Endocrine Society
- American College of Toxicology
- Society of Toxicology
- Western Pharmacology Society
- Sigma Xi
- National Society for Medical Research
- International Union of Toxicology
- Midwest Pharmacology Society
- Canadian Toxicology Society
- Teratology Society
- Pharmacological Society of Canada
- Gulf Coast Society of Toxicology
- Midwest Society of Toxicology
- National Association Biomedical Research
- Association Academic Health Centers
- American Chemical Society, Division Chemical, Health & Safety
- Texas Society of Biomedical Research
- U.S.-Mexico Border Public Health Association
- Society for Basic Urologic Research
- American Council Government Industrial Hygiene

**ADMINISTRATIVE EXPERIENCE**

| | |
|---|---|
| 1973-1975 | Assistant Dean, West Virginia University School of Medicine |
| | Fiscal & Administrative Officer, West Virginia University School of Medicine |
| 1973-1975 | Promotion and Tenure, West Virginia University School of Medicine |
| 1973-1982 | Chief Grants and Contracts Officer, West Virginia School of Medicine |
| | Affirmative Action Liaison, West Virginia School of Medicine |
| | Biomedical Research Grant Support Officer, West Virginia University School of Medicine |
| | Facilities and Scheduling, West Virginia School of Medicine |
| | West Virginia University School of Medicine, Executive Faculty |
| | West Virginia University School of Medicine, Admissions Committee, Vice Chairman |
| | West Virginia University School of Medicine, Promotions Committee, Chairman |
| | West Virginia University School of Medicine, Educational Program Committee |
| 1973-1982 | West Virginia University Medical Center Planning Committee, Chairman |
| 1974-1982 | West Virginia University School of Medicine, Building Committee, Chairman |
| 1974-1982 | West Virginia University School of Medicine, Learning Resources Committee |

**ADMINISTRATIVE EXPERIENCE (Cont'd)**

| | |
|---|---|
| 1975-1982 | Academic Review, West Virginia University School of Medicine |
| 1975-1982 | Associate Dean, West Virginia University School of Medicine |
| 1976 | American Association of Medical Colleges Executive Development Program (M.I.T. Sloan School of Management) |
| 1976-1982 | West Virginia University School of Dentistry, Faculty Council |
| 1977-1982 | West Virginia University School of Medicine, Financial Aids Committee |
| 1978-1982 | West Virginia University School of Medicine, Computer Users Committee |
| 1978-1982 | West Virginia University Hospital-Medical School Liaison Committee |
| 1979-1982 | National Science Foundation, Chairman-Committee to Stimulate Competitive Research in the State of West Virginia (NSF University - Industry Grant Program) |
| 1980-1982 | West Virginia University Medical Center (rDNA), Chairman- Biohazards Committee |
| 1982-1987 | Vice President, Corporate R&D, Baxter Healthcare Corporation |
| 1982-1985 | Life Sciences Research Laboratories, Planning and Building Committee, Baxter Healthcare Corporation |
| 1982-1986 | Senior Management Council, Baxter Healthcare Corp. |
| 1985 | Executive College, The Quality College, Phillip Crosby Associates, FL |
| 1988-1998 | Executive Committee, University of Texas Health Science Center at San Antonio(UTHSCSA) |
| 1988-1998 | Committee on Committees, University of Texas Health Science Center at San Antonio |
| 1988-1998 | Faculty, Graduate School, University of Texas Health Science Center at San Antonio |
| 1988-1998 | Executive Council, Medical School, The University of Texas Health Science Center at San Antonio, ex officio |
| 1988-1998 | Executive Council, Dental School, The University of Texas Health Science Center at San Antonio, ex officio |
| 1988-1998 | Toxicology Consortium, San Antonio Academic and Research Institutes |

**SELECTED LIST OF PAST AND PRESENT CONSULTANTSHIPS AND ADVISORY ROLES**

- H.E.W. - Health Manpower Branch, Region III
- Environmental Protection Agency
- National Cancer Institute, Committee on Carcinogenesis
- University Park Press, Baltimore, Maryland
- Mason Research Institute, Worchester, MA
- ASHA-PMA Lecturer on Drug Abuse
- Encyclopedia Britannica
- Editorial Board J. Toxicology & Appl. Pharmacology, 1973-1985;Specialty Edit. 2001-
- Editorial Board, J. Toxicology & Environmental Health, 1978-1993
- Editorial Board, Perspectives in Toxicology, Raven Press, New York, New York, 1980
- Editorial Board - Fundamental & Applied Toxicology, 1983-1990
- Editorial Board, Technomics Publishing Company (Health Science Division), 1977-1979
- Editorial Board, Target Organ Toxicity Series, Taylor & Francis, Phil, PA, 1989-Present
- Editor-in-Chief, Journal Toxic Substances, Francis & Taylor Publishers, 1993-1997
- Editor, Emeritus, Toxic Substance Mechanisms Journal, 1998 -
- Editorial Board, Food & Chemical Toxicology, 1993-Present
- Editorial Board, Advances in Pharmacology, 1994-Present
- Ad hoc Reviewer - Journal of Animal Science
- Ad hoc Reviewer - Proceedings Society Experimental Biology and Medicine
- Ad hoc Reviewer - Science
- Ad hoc Reviewer - American J. School Health
- Ad hoc Reviewer - American J. Physiology-
- Ad hoc Reviewer - Journal of National Cancer Institute
- Ad hoc Reviewer - The Prostrate
- Ad hoc Reviewer - Andrology
- Ad hoc Reviewer - New England Journal of Medicine
- Ad hoc Reviewer - Toxicology Letters
- Ad hoc Reviewer - Journal Pharmacology & Experimental Therapeutics
- Ad hoc Reviewer - Journal of Reproduction & Fertility
- Ad hoc Reviewer - Cell Biochemistry and Function
- Ad hoc Reviewer - Life Sciences
- Clinical Pharmacology - Texas Allergy Research Foundation, Houston, TX
- Clement Associates, Inc. Scientific Regulatory Consultants, Washington, DC
- World Health Organization (WHO) - Narcotic Division, Geneva, Switzerland
- National Institute Arthritis, Metabolic, and Digestive Diseases
- Union Carbide Corporation, Danbury, CT
- American Public Health Association, Washington, DC
- Urban & Schwarzenberg Medical Publishers, Baltimore, Maryland
- National Science Foundation - Regulatory Biology Program
- Professional Consultants in Occupational Health, Inc., Washington, DC
- National Toxicology Program (NTP), Board of Scientific Counselors
- EXXON Corporation, Newark, NJ
- Syntex Research, Palo Alto, CA
- Bell Laboratories, East Millstone, NJ
- IBM Corporation, White Plains, NY
- Ciba-Geigy Pharmaceuticals, Greensboro, NC
- Department of Defense, Review Panel, Defensive Toxins, Ft. Detrick, MD
- Advisory Board, School of Engineering (Biomaterials), Clemson University, Clemson, SC
- American Medical Association-Drug Evaluation
- Advisory Board, John Jay College of Criminal Justice Research & Training Center, CUNY
- National Board of Advisors, University of Arizona College of Pharmacy
- NutraSweet, Inc., Deerfield, IL
- Monsanto Company, St. Louis, MO

**SELECTED LIST OF PAST AND PRESENT CONSULTANTSHIPS AND ADVISORY ROLES (Cont'd)**

- Intermedics, Inc., Freeport, TX
- United Oil Products (UOP), Des Plaines, IL
- Rohm & Haas, Philadelphia, PA
- Osteo SA, Board Member
- Board of Trustees, International Life Sciences Institute-North American, Washington, DC
- Advisory Board, Journal of Environmental & Nutritional Interactions
- Publications Committee, Nutrition Reviews
- Advisory Board, San Antonio Medical Gazette
- Advisory Panel: Center for the Study of Environmental Endocrine Effects, Wash., DC
- Novartis, Geneva, Switzerland
- Gerber (Sandoz), Freemont, MI
- Mead-Johnson, Evansville, IN
- Bristol-Myers Squibb, Evansville, IN
- Osteo Screen, Inc. Board Member, 1997-Present
- International Myco Biologics, Board Member
- Center for Human Reproduction, Washington, DC
- Archer Daniel Midland, Decatur, IL

**SELECTED LIST OF PAST AND PRESENT COMMITTEES AND OFFICES**

| | |
|---|---|
| 1962-1963 | Secretary - Virginia Academy of Sciences, Medical Sciences |
| 1962-1964 | Research Fellowship Committee, University of Virginia |
| 1964 | President - Virginia Academy of Sciences, Medical Sciences |
| 1965-1967 | Secretary-Treasurer, Society of Sigma Xi - Creighton University |
| 1967-1969 | Curriculum Committee, West Virginia University School of Medicine, Chairman |
| 1967-1973 | Director of Graduate Studies in Pharmacology (WVU)<br>Co-Director, USPHS Training Grant in Pharmacology (WVU) |
| 1967-1982 | Faculty of Reproductive Physiology, Institute of Biological Sciences (WVU) |
| 1968-1974 | Medical Center Long-Range Planning Committee (WVU) |
| 1968-1975 | Cancer Fellowship and Research (WVU) |
| 1968-1980 | Radiation and Isotope Committee (WVU) |
| 1968-1982 | Thesis Committee (WVU) |
| 1968-1984 | Dissertation Committees (VWU) |
| 1969 | Secretary, Society of Sigma Xi - West Virginia University |
| 1969-1971<br>1973-1976 | Faculty Senate (WVU) |
| 1969-1973 | Medical School Promotions Committee (WVU), Chairman 1970-1973 |
| 1969-1973 | Medical School Admissions Committee( WVU), Vice Chairman, 1970-1973 |

**SELECTED LIST OF PAST AND PRESENT COMMITTEES AND OFFICES (Cont'd)**

| | |
|---|---|
| 1970-1971 | Faculty Senate Committee( WVU), Membership and Constituencies |
| 1970-1975 | American School Health Association, Committee on Drug Abuse |
| 1970-1978 | Faculty Promotions & Tenure Committee, Department of Pharmacology ( WVU) |
| 1970-1979 | Pre-Medical Advisory Group ( WVU) |
| 1970-1979 | Basic Science Administrator for West Virginia University Comprehensive Cancer Center |
| 1972-1974 | President's ( WVU) Task Force Committee on North Central Accreditation |
| 1972-1974 | Faculty Promotions and Tenure WVU, School of Pharmacy) |
| 1972-1974 | President's ad hoc Council for West Virginia Univ. Research and Graduate Education |
| 1972-1974 | Inter-Disciplinary Advisory Committee - Masters Program in Nursing( WVU) |
| 1975 | Graduate Faculty, Kent State University |
| 1975; 1991 | Board of Examiners, University of Madras, India |
| 1975 | Board of Examiners, University of Ottawa, Canada |
| 1978 | Search Committee, University Comptroller ( WVU), Chairman |
| 1977-1978 | Research Strategy Committee (WVU), Chairman |
| 1977-1979 | University Energy Committee ( WVU) |
| 1978 | By-Laws Committee, West Virginia University School of Medicine |
| 1980-1982 | Post-Doctoral Training Grant - Endocrinology (WVU) |
| 1982 | Technical/Scientific Awards Committee, Baxter Healthcare, R&D |
| 1982 | Professional Career Planning, Baxter Healthcare, R&D |
| 1985 | Biotechnology Education Task Force, Center for Occupational Research & Development |
| 1986 | National Science Foundation, Panel on Industry & Technology |
| 1988 | Chair, Ad Hoc Committee on Research Contracts, University of Texas System |
| 1989 | Search Committee, Dean, School of Medicine ( UTHSCSA) |
| 1989 | Southern Association of Colleges and Schools (SACS) Steering Committee |
| 1989 | Search Committee, Chair, Director for Institutional Review Board ( UTHSCSA) |
| 1989-1992 | Chair, Texas Education Opportunity Plan (TEOP) (1989-1992) (UTHSCSA) |

**SELECTED LIST OF PAST AND PRESENT COMMITTEES AND OFFICES (Cont'd)**

| | |
|---|---|
| 1988-1998 | Academic Computing Committee ( UTHSCSA) |
| 1988-1998 | Committee on Committees ( UTHSCSA) |
| 1988-1998 | Library Committee ( UTHSCSA) |
| 1988-1998 | Educational Resources Advisory Committee ( UTHSCSA) |
| 1988-1998 | Institutional Animal Care & Use Committee ( UTHSCSA) |
| 1988-1998 | International Relations Committee ( UTHSCSA) |
| 1996-1998 | Chair, Conflict of Interest Committee ( UTHSCSA) |

**PUBLICATIONS, BOOKS & CHAPTERS, AUDIO-VISUAL MATERIALS, & ABSTRACTS**

**PUBLICATIONS**

Searle GD. et al.: Effect of 2450 Megacycle Microwaves in Dogs, Rats and Fruit Flies. Biological Effects of Microwave Radiation 1:1 87, 1961.

Thomas, JA: Carbohydrate Metabolism in Patients with Rheumatoid Arthritis as Determined by Oral and IV Glucose Tolerance. M.A. Thesis, University of Iowa, 1958.

Thomas JA: Modification of Glucagon-Induced Hyperglycemia by Various Steroidal Agents. Metabolism 12:207, 1963.

Thomas JA: Norethandrolone-induced Changes in Hepatic Phosphorylase Activity. Metabolism 13:63,1964.

Thomas JA and Strauss AJ: The Effect of Steroids on Mouse Sex Accessory Fructose Levels. Acta Endocrinologica (Copenhagen) 48:619, 1965

Assaykeen TA and Thomas JA: Endogenous Histamine in Male Organs of Reproduction. Endocrinology 76:839, 1965.

Thomas JA and Andrews RV: Fructose Levels in Sex Accessory Organs of Mature Golden Hamsters. Endocrinology 77:1147, 1965.

Thomas JA and Knych ET, Jr.: Antagonistic Action of Norethynodrel on the Testosterone Dependent Process of Fructose Formation in Mouse Sex Accessory Organs. Acta Endocrinologica (Copenhagen) 51:244,1966.

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Smith MT and Thomas JA: Histopathology of Human Prostate (108-2" x 2" photomicrograph set of light and EM slides). Westport CN, Technomics Publishing Co. (Hlth.Sci. Div.), 1977.

SUBMISSION END

AM

## Lubin, Lisa

**From:** Jim Griffiths
**Sent:** Friday, May 07, 2004 5:12 PM
**To:** Lubin, Lisa
**Cc:** Alan Hood; DP; GB; Mihalov, Jeremy J.
**Subject:** RE: GRAS Notice No. GRN 000144 (AMP)

Dear Ms. Lubin,

No, the pyrimidines were not part of the calculation as a re-examination of the Kojima (1974) paper indicates that only purines were part of the description and evaluation:

AMP
GMP
IMP
XMP

and their bases, nucleosides, nucleotides and nucleic acids.

Please let me know if this is a sufficient response at this juncture. For any further info, can you also copy Dr. Alan Hood (ahood@burdockgroup.com) as I will be out of the office next week and he is quite proficient in consumption analyses.

Warm regards,

Jim

-----Original Message-----
**From:** Lubin, Lisa ]
**Sent:** Thursday, May 06, 2004 10:42 AM
**To:** [redacted]
**Cc:** Mihalov, Jeremy J.
**Subject:** GRAS Notice No. GRN 000144 (AMP)

Dear Dr. Griffiths:

In reviewing GRAS Notice No. GRN 000144, Agency scientists had a few questions regarding the section on estimated daily intake of AMP in Linguagen's GRAS Panel Report. In your calculation of estimated daily intake of AMP, you include a current daily intake from the diet for purines. Can you elaborate further on how you define "purines"?

We note that you cite the publication Kojima, 1974 in this section, which describes purines (p. 189) as "purine bases, nucleosides, nucleotides, and nucleic acids." Since this definition of purines includes nucleic acids, we also ask if pyrimidines are, therefore, part of your current daily intake estimate?

We look forward to your reply.

Sincerely,

Lisa F. Lubin, MS, RD
Division of Biotechnology and GRAS Notice Review
Office of Food Additive Safety
Center for Food Safety and Applied Nutrition
Food and Drug Administration
5100 Paint Branch Parkway, HFS-255
College Park, MD 20704